The role of the new Russian anti-bioterrorism centres

KRISTINA S. WESTERDAHL AND LENA NORLANDER

FOI
Defence Research Agency
NBC Defence
SE-901 82 Umeå

Phone: +46 90 10 66 00
Fax: +46 90 10 68 00

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Kristina S. Westerdahl and Lena Norlander

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Abstract

Russian counter-measures to bioterrorism include the establishment of two designated lead centres: The Centre of Special Laboratory Diagnostics and Treatment of Especially Dangerous and Exotic Infectious Diseases (CSDT) at the Ministry of Defence Virology Centre in Sergiev Posad, and the Federal Interagency Centre (FIAC) at the Volgograd Anti-Plague Institute, subordinate to the Ministry of Health. By selecting well-established institutes with experience of countermeasures to diseases caused by natural and deliberate spread of pathogens, resources such as qualified staff, equipment and strain collections were already in place. In purpose to understand the framework of the new centres, the past two decades' scientific publications of the mother institutes are reviewed in depth and the areas of competence are described for each facility. Additionally, the reported activities of the centres are assessed. The two centres are independent from each other, established by separate orders and funding. The aims and areas of activities are complementary. The available information indicates that CSDT takes active part in domestic outbreaks. The lack of information on FIAC makes the assessment of its role impossible.

According to the publications lists 1985-2004 both institutes have a frequent but low publication rate and several collaborating institutes in Russia. There is a continuous interest in viruses and bacteria that have been in focus for decades. The Virology Centre/CSDT has an impressive knowledge in several of the most dangerous viruses known and a high technical competence, modern equipment, and techniques in molecular biology. The Volgograd institute and centre seems to have more traditional research techniques for studies of bacteria, albeit with knowledge of a limited set of bacteria. The scientists have an adequate experience in areas that are relevant for the FIAC.

Keywords

Bioterrorism, terrorism counter-measures, biological weapons, Russia, Sergiev Posad, MoD Virology Center, Volgograd Anti-Plague Institute

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Rollen för de nya ryska centren mot bioterrorism

Sammanfattning

Som en del i de ryska åtgärderna för att öka beredskapen mot bioterrorism har två center inrättats: Centrum för speciell laboratoriediagnostik och behandling av speciellt farliga och främmande infektionssjukdomar (CSDT) vid Försvarsministeriets virologiska institut i Sergiev Posad och ett Federalt samordningscentrum (FIAC) vid Volgograds antipestinstitut, organisatoriskt under Hälsovårdsministeriet. Genom att förlägga centren till väletablerade institut som utvecklat skydd mot sjukdomar orsakade både av naturliga och avsiktligt utspridda smittämnen, finns kunnig personal, lämplig utrustning och stamkollektioner tillgänglig för de nya centrens verksamhet. I avsikt att få en inblick i centrens förmågor och måluppfyllelse har forskningsinstitutens publikationer under två decennier utvärderats, deras kompetenser beskrivits och centrens aktiviteter har granskats.

De två centren agerar oberoende av varandra, de inrättades av olika huvudmän och har olika finansiärer. Deras målsättningar och aktivitetsområden kompletterar varandra. Tillgänglig information tyder på att CSDT tar aktiv del i sjukdomsutbrott i Ryssland, medan bristen på information kring FIAC omöjliggör en utvärdering. Båda instituten har en lågfrekvent men stabil publikationsfrekvens 1985-2004 och ett tiotal samverkande institut vardera.

Forskningsfokus är oförändrat under hela perioden; i stort sett samma virus och bakterier återfinns i publikationerna. Det virologiska institutet/CSDT har en imponerande kunskap om flera av de idag kända farliga virus, hög forskningskompetens, modern utrustning och molekylärbiologisk metodik. Volgograds institut och center har en mer traditionell kunskapsbank och tekniker för studier av bakterier. Kunskapen är begränsad till ett fåtal bakterietyper. Forskarna har dock erfarenheter som är relevanta för den verksamhet som ålagts FIAC.

Nyckelord

Bioterrorism, motåtgärder, biologiska vapen, Ryssland, Sergiev Posad, Försvarsministeriets virologiska center, Volgograd antipestinstitut

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Executive Summary

The use of weapons of mass destruction (WMD) in state-to-state conflicts has been an assessed risk and now there is an additional, broader and less defined threat – the use of WMD by terrorists. Various approaches to counter-act bioterrorism are seen in different countries. Russian concern with terrorism in general in the 1990s led to counter-measures to bioterrorism, among them the establishment in 1999 of two designated lead centres: The Centre of Special Laboratory Diagnostics and Treatment of Especially Dangerous and Exotic Infectious Diseases (CSDT) at the Ministry of Defence (MoD) Virology Centre in Sergiev Posad, and the Federal Interagency Centre (FIAC) at the Volgograd Anti-Plague Institute (API), subordinate to the Ministry of Health (MoH).

The mother institutes of the new centres are well-established research institutes and were among the foremost in Soviet research on dangerous diseases. They also contributed to the protection against natural outbreaks and preparedness for biological weapons attacks. To better understand the framework of the new centres, the scientific publications of the mother institutes are reviewed in depth for the past two decades and the areas of competence are described for each facility.

The two centres are independent from each other, established by separate orders and funded separately. The aims and areas of activities are different and could be viewed as complementary, and only one example of cooperation between the centres was found.

The Virology Centre is a military facility and “closed”, in the sense that there are no foreign visitors, nor does the centre staff have any collaborations with foreign organisations, but it has a wide net of contacts in Russia with many co-authored scientific papers. The centre has continuously produced open papers, resulting in a certain degree of transparency. However, additional research results are classified as this institute is subordinate to the MoD and works on means of protection against biological weapons.

It is obvious from the survey of over 100 scientific publications and presentations from the Virology Centre/CSDT that it has an impressive knowledge in some of the most dangerous viruses known, and also methods and equipment for studying such viruses. The centre has a broad range of viral pathogens under investigation, including the Marburg, Ebola and Lassa viruses. The resources of the Virology Centre - a high technical competence, modern equipment, and techniques in molecular biology - are also assigned to the CSDT.

The Volgograd API is an open facility and has a number of collaborating institutes in Russia, Bulgaria and the Ukraine. According to the over 120 reviewed papers, the API seems to have more traditional research techniques for studies of bacteria that most likely reflects a staff of skilled classical microbiologists, albeit with knowledge of a limited set of bacteria. The scientists of this institute have an adequate experience in areas that are relevant for the FIAC.

The two mother institutes have routinely used animals infected by aerosols. This requires special equipment and know-how. There is also a marked interest in aerosol techniques and stability of aerosol particles, e.g. use of carriers. The facilities for animal experiments seem to be extensive and suited for various species, at the Virology Centre also including primates. At the API, a new aerosol laboratory was built in the mid-1990s.

The new centres were evaluated as to how they fulfil the original intentions, i.e. as outlined in the decrees. The CSDT performs laboratory diagnostics, isolates, characterises and stores pathogens, and there are several examples of laboratory and research work. The CSDT can also provide hospital care for patients having dangerous diseases. In contrast, little is known on its evaluation of epidemiological measures and improvements in prevention and liquidation of especially dangerous diseases. Reportedly, the CSDT has processed many pathogen samples, and has had the opportunity to create an impressive strain collection of new and re-emerging pathogens. A corresponding assessment of the FIAC is not possible due to the lack of information on its activities, maybe because of the strong focus on educational activities that would not be widely reported in media or scientific publications. Underfunding could also contribute.

By selecting two institutes aimed at pathogenic viruses and rickettsia (the Virology Centre) and at bacteria and fungi (the Volgograd API), respectively, the entire scale of pathogens should be covered. This is certainly true for the Virology Centre/CSDT, but can be questioned for the Volgograd API/FIAC as this facility has been working with a very limited set of bacteria.

The research directions for the two centres and their mother institutes have not changed significantly since 1990, although bioterrorism is now a high priority in Russia. There is more of a continuous interest in viruses and bacteria that have been in focus for decades. Only two viruses and one bacterium from the priority lists are among the most frequent organisms in the publications from the two institutes: Variola and Marburg virus and Burkholderia mallei. According to the publications, the Ebola, Variola and Marburg viruses as well as the two Burkholderia species causing glanders and melioidosis are the top five organisms to be used as biological warfare agents by non-state or state actors. Neither of these pathogens is a real domestic problem in Russia, with the possible exception of Burkholderias that could be a veterinary concern.

Contrary to corresponding research facilities in the West, the scientific production related to counter-measures to bioterrorism, i.e. new vaccines, and identification and treatment means and methods, from these Russian centres/institutes is approximately halved, measured as openly published papers. The Virology Centre focuses more on vaccines, treatment and identification than other measures. At the Volgograd API, identification and detection seem to be important issues. Research on vaccine development and pathogenesis is more frequent in recent publications. It is possible that some of the scientific production is classified due to the perceived threat from bioterrorism.

The new centres are civilian as well as their aims and activities. However, it cannot be completely ignored that their respective mother institutes were involved in the world’s largest offensive bioweapons programme run by the Soviet Union. Russia is a states party to the Biological and Toxin Weapons Convention and has denied the existence of any offensive programme and biological weapons. In this context, the unchanged focus regarding pathogens studied, and the expertise in aerosol and research that can contribute to both defensive and offensive aims at the two new centres and their mother institutes are notable.

In conclusion, it was a logic measure to incorporate the new centres in well-established institutes with experience in development of measures to prevent diseases caused by natural and deliberate spread of bacteria and viruses. Resources in terms of qualified staff, equipment and strain collections were already in place. The know-how of these institutes is unique and thus a splendid source for the development of counter-measures to bioterrorism. However, it is not

possible to make a full evaluation of the outcome of the centres´ activities because there is not enough information on hand. The available information indicates that especially the CSDT takes active part in domestic outbreaks. This gives valuable experience for handling potential future outbreaks, both natural and after the deliberate spread of infectious agents. It is more doubtful whether FIAC fulfils its role. In future studies of these centres, their research priorities and whether any changes take place will be of interest.

Contents

Introduction

The use of weapons of mass destruction (WMD)[1] in state-to-state conflicts has been an assessed risk for decades. The sarin attack in the Tokyo underground in 1995 verified the existence of an additional, broader and less defined threat – the use of WMD by terrorists. In the years following the disclosure of the ambitions of the Japanese religious cult to produce not only chemical agents but also biological agents, the world realised the need for counter-measures to biological and chemical terrorism. The cult had followers also in Russia. The anthrax letters in the US in 2001 further spurred a public debate on biological terrorism both in political and scientific fora. This, in turn, has led to measures being taken to prevent and manage incidents of this type, until 2005 totaling in the neighbourhood of 8 billion US dollars.[2] The US has made far-reaching efforts to meet the threat from terrorists. The Proliferation Security Initiative (PSI) is one example, a partnership of 15 countries around the world, including Russia. The G8 dedicated the Kananskis summit to this issue.[3]

On the national level various approaches are seen in different countries. In the US, nationa-wide training, new high-security laboratories, planning and research, as well as new legis-lation are among the measures taken. The EU focuses on European cooperation, strengthening national capabilities, developing collective capabilities and international partnerships.[4]

The aim of this report is to study the national counter-measures to bioterrorism in Russia. Measures taken in the past decade will be described briefly, followed by a detailed analysis of the two lead centres against bioterrorism in Russia. These are based at two well-established research institutes in Russia, the Ministry of Defence (MoD) Virology Centre in Sergiev Posad and the Volgograd Anti-Plague Institute subordinate to the Ministry of Health (MoH). Historically, these institutes were among the foremost in Soviet research on dangerous dis-eases and contributed to the protection against natural outbreaks and preparedness for biologi-cal weapons (BW) attacks. The Soviet Union ran the world's largest offensive bioweapons programme, where these research facilities also played a role.[5, 6]

To better understand the framework and resources of the new centres, the scientific publica-tions of the mother institutes, here defined as the papers where the first author is affiliated with the centre/institute, are reviewed in depth for the past two decades. The papers were retrieved from the literature databases PubMed and BIOSIS that include many peer-reviewed Russian journals. That the retrieved papers indeed covered the publications from the Virology

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1 Nuclear, chemical and biological weapons

2 Forsberg, Å. and Norqvist, A. "Skydd mot bioterrorism – amerikansk storsatsning" [Protection against bioterrorism – American major investment], BC-Bulletinen, No. 14, December 2005, URL <http://www.foi.se/upload/bc-bulletinen/BC-bulletinen14-maj-2005.pdf>

3 The Kananaskis Summit Chair's Summary, URL <http://www.g8.gc.ca/2002Kananaskis/chairsummary-en.asp>, accessed 16 March 2006

4 URL <http://ue.eu.int/uedocs/cms_Data/docs/pressdata/en/jha/87257.pdf>, accessed 10 January 2006

5 Ken Alibek. Biohazard. Hutchinson (London), 1999

6 I V Domaradsky and W. Orent. The memoirs of an inconvenient man: Revelations about the biological weapons research in the Soviet Union. Critical Reviews in Microbiology, Vol 27, No. 4, pp. 239-266, 2001

Centre was verified by comparison to the Centre's own list of publications.[7] Based on these publications, areas of competence can be identified and are described for each facility.

By comparison, there is much less known about the activities of the two new centres since their establishment in 1999. The available information retrieved from open sources is presented. Finally, the new centres are discussed in terms of their capacities, their priorities in countering bioterrorism and their places in the Russian system. An attempt to evaluate how they fulfil the decreed intentions is also made.

[7] Lukina RN, Lukin EP, Bulavko VK (eds.). Dostiyny izvestnosti [Deserving Fame]"; 50th anniversary of the Virological Centre of the MoD. Council of Veterans at the Virological Centre of the MoD, 10 January 2004

Bioterrorism counter-measures

Bioterrorism counter-measures in Russia are taken in the wider context of preventing and countering terrorism. The first armed conflict in Chechnya was a main impetus for Russia to step up measures to counter terrorism.[8] But it can also be argued that anti-terrorism is one more pawn in Russian politics today.[9] It has been used in Putin's platform of power and in Russian foreign relations since the autumn of 2001. In similar, the counter-measures to bio-terrorism are a focus of interest and activities *per se*, but may also be a new arena for members of the former BW complex.[10]

Briefly, the view of the threat from bioterrorism in Russia is that it is a real threat, i.e. there is a high probability that attack(s) will occur, and in fact, the likelihood is increasing. These arguments are based on international incidents.[11] There are very few who publicly express doubts in the likelyhood of a bioterrorist attack. Valeriy Spirande, the deputy director at the Russian Agency for Munitions, in spring 2003 said that the greatest risk would be to the criminal who steals micro-organisms, and that it was not possible to produce biological weapons in a kitchen.[12] So far, no bio-incidents have been reported from Russia, except hoax anthrax letters in late 2001.[13]

There is a list ranking possible biological agents based on complex scientific information (Appendix A).[14] The targets are much less detailed. Food production[15], transports[16] and facilities handling dangerous pathogens[17] are considered in the counter-measures. The only group specifically mentioned as potentially attacking Russia with biological agents are the Chechen separatists[18, 19, 20]. There have been rumours now and then of biological weapons in

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8 Stepanovna E. "Russia's Approach to the fight against terrorism", in Hedenskog, J. et al. (eds.) "Russia as a Great Power", London, New York: Routledge, 2005, pp.301-322

9 Baev, P.K. "Counter-terrorism as a building block for Putin's regime", in Hedenskog, J. et al. (eds.) "Russia as a Great Power", London, New York: Routledge, 2005, pp.323-344

10 Most of those who in open media debated bioterrorism before autumn 2001 had past connections with the Soviet offensive biological weapons programme. Lindblad et al. 2005. Russian biological and chemical weapons Capabilities: Future Scenarios and Alternatives of Actions. FOI-R--1561----SE, 2005

11 Kondrik et al., 2003

12 Poroskov, N. 'We were not going to use biological weapons', Vremya Online, 24 April 2003

13 Alexandr Litvinov. Volgograd family received funny powder in mail. Komsomolskaya Pravda, 4 October 2001, URL <http://www.kp.vgg.ru/TEXT/01_10_04/05.html>, accessed 20 February 2004

14 Kondrik EK, Volkov VYa, Kavyzina LI, Staritsyn NA, Urakov NN. "Analytical Basis of the Concept of Biological Security." Obolensk, 2003

15 Safanov, G.A. and Gavrilov, V.A. Problems of biological security in agriculture. Veterinariya, No. 11, pp. 3-5, November 2002 .

16 For example biodetectors in the Moscow metro: Metro Head Says 2 Blasts Prevented. The Moscow Times, p. 3, 23 September 2005, URL <http://www.themoscowtimes.com/stories/2005/09/23/014-print.html>, accessed 23 September 2005

17 "Biological Terror. Real Not Imaginable Threat." RIA Novosti, 28 January 2004

18 Elena Mikhaylina. A feverish zone - the secrets of the numbered Zagorsks. Moskovskiy Komsomolets, 8 December 2004, URL <http://www.mk.ru/numbers/1406/article44343.htm>, accessed 16 December 2004

19 "Khattab wants to teach Russia a biology lesson." Agency WPS, 27 October 1999

20 Biological warfare instructions found on Chechen rebels – interior minister. BBC Summary of World Broadcasts, 1 November 1999

Chechnya[21, 22, 23] and statements to the opposite.[24, 25] However, it is important to remember that menacing statements in the media are to some extent part of the Chechen theatre of war.

The first armed conflict in Chechnya 1994-95 was a main impetus for Russia to step up measures to counter terrorism.[26] The Federal Antiterrorist Committee (FAK) was formed in 1997[27], and since then Russia has systematically taken new measures against terrorism by adopting legislation, and developing and implementing various counter-measures. Several counter-measures to bioterrorism appeared in 1997-2004.

According to G.G. Onishchenko, State Sanitary Surgeon and head of the Federal Service for Consumer Rights and Human Wellbeing (Rospotrebnadzor) ”a considerable part of the scientific and organisational measures to counter bioterrorism are conducted in Russia within the framework of the existing system of measures against infectious diseases.”[28] More specifically, the main measures in 1999-2003 were:[29, 30]

- FAK developed and refined a Concept of Antiterrorist Activities of Federal Organs in the area of Protecting the Environment and the Health of the Population;
- an interdepartmental working group for questions on the protection of the population, agricultural animals and plants against possible use by terrorists of biological, chemical and other means of mass destruction, was formed;
- a Federal Inter-Agency Centre (FIAC) was created for training of specialists, evaluating methods of identification at the Volgograd Anti-Plague Institute;
- a Centre of Special Laboratory Diagnostics and Treatment of Especially Dangerous and Exotic Infectious Diseases (CSDT) was created on the basis of the Virology Centre of the Military Institute of Microbiology (at Sergiev Posad);

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21 Biological warfare instructions found on Chechen rebels - interior minister. BBC Summary of World Broadcasts, 30 October 1999

22 “The Russians used bacteriological weapons in the Chechen Republic”, Kavkaz-Tsentr, 15 August 2000, URL <http://www.kavkaz.org/vajno/virus.htm>, accessed 24 August 2000

23 “Military Chief Says Blueprints For Dirty Bombs Found In Chechnya”, Ekho Moskvy,

24 MARK MacKINNON. Will use any tactic, Chechen warlord warns. The Globe and Mail, 2 November 2004, URL <http://www.theglobeandmail.com/servlet/ArticleNews/TPStory/LAC/20041102/CHECHEN02/TPInternational/Asia>, accessed 3 November 2004

25 Yastrzhembskiy Doubts Chechens Possess Biological Weapons. Interfax, 28 April 2000

26 Stepanovna E. “Russia’s Approach to the fight against terrorism”, in Hedenskog, J. et al. (eds.) ”Russia as a Great Power”, London, New York: Routledge, 2005, pp.301-322

27 Government of the Russian Federation, 'Decree No. 1302 of the Government of the Russian Federation about a Federal Antiterrorist Committee', 6 November 1998

28 Onischenko, G.G. et al. 'Bioterrorism: A national and global threat', Vestnik Rossiyskoy Akademii Nauk, Vol. 73, No. 3 (March 2003), pp. 195-204

29 Onishchenko, G.G. 'Bioterrorism counteractions: The strategy of the national health care', Vaktsinatsia, Vol. 21, No. 3 (May-June 2002)

30 Yevstigneev, V.I. 'Biological Weapons and Problems of Ensuring Biological Security', Paper presented at the Moscow Institute of Physics and Technology, 25 March 2003

- to promote growth of the scientific-biotechnological potential the programme ”Zashchita”[31] was adopted; and
- a policy was developed regarding cooperation among the Russian Federation Ministry of Health, Russian Federation Ministry of Internal Affairs, and Russian Federation Federal Security Service (FSB) in monitoring the status of public health and epidemic control in facilities where masses of people are concentrated and in actions during emergencies caused by terrorist acts.

In addition to these, recently, a new system for biosecurity is being developed in Russia, but there is very scant information about it, except that it will involve the State Scientific Centre Vector (Novosibirsk) and the State Scientific Centre for Applied Microbiology (Obolensk),[32] and. judging by the funding expected for Vector, this system apparently is heavily funded.[33] As far as is known, it does not involve the two new anti-bioterrorism centres in Sergiev Posad and Volgograd.

Over time, the counter-measures can be seen to have evolved from a conceptual and national level to ”concretisation” and implementation at the local level. Some examples are: Training bio-incidents by the regional security services[34], stock-piling vaccines[35], and improving control over facilities handling dangerous pathogens[36] and food and drinking water.[37]

The bioterrorism counter-measures require cooperation and coordination between many sectors in society. This is obvious in Russia where about a dozen ministries and agencies are concerned. The Russian approach to handle the bureaucracy involved is to form interdepart-mental committees.[38] For example, the FAK has a working group (No.3) on ”the protection of the population, agricultural animals and plants against possible use by terrorists of biological, chemical and other means of mass destruction”, with representatives from e.g. the MoH and the Federal Sanitary-Epidemiological Monitoring Service (now probably the Federal Service for Consumer Rights and Human Wellbeing), MoD, Ministry of Interior,

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31 The full name of the programme is “The creation of methods and means of defending the population and environment against dangerous and extremely dangerous pathogens in natural and man-made emergency situations from 1999 to 2005”, 2 July 1999, Government of the Russian Federation. Resolution No. 737, 2 July 1999. The programme is often called ”Zashchita” (”Protection”) and as is evident from its full name it encompasses protection against both diseases due to natural outbreaks and of public health concern, as well as acts of bioterrorism. The involved facilities, under e.g. the MoH and the MoD, were to develop and produce diagnostics, vaccines and preparations for treatment. It is unclear if the programme received all of the planned funding of 1.37 billion roubles.

32 Novosibirsk should take a notable place on a resource map of biosafety of Russia, the Minister of Education and sciences of the Russian Federation count Andrey Fursenko. Sibir RIA, 12 January 2005, URL <http://ria-sibir.ru/viewnews/4023.html>, accessed 17 January 2005

33 Substantive Increase in State Funding Slated for "Vektor" Virology Centre. The Russian BW Monitor, 12 January 2005, URL <http://www.russianbwmonitor.com>

34 In Primorski Krai excercises on prevention of acts of terrorism will regularly be carried out. Regions.ru, 18 February 2005, URL <http://www.regions.ru/article/any/id/1745637.html>, accessed 22 February 2005

35 Russia's Preparedness for Biological Attack. The Russian BW Monitor, 14 October 2004

36 In the Novgorod area are taken additional measures on counteraction to threat of biological terrorism. RIA Novosti, 2004, URL <http://rian.ru/defense_safety/20040924/690792.html>, accessed 25 November 2005

37 About measures on counteraction to biological terrorism in Tomsk area. TU Rospotrebnadzora po Tomskoy oblast, 2005, URL <http://snadzor.tsu.ru/Postanovlen/27_4_terror.htm>, accessed 25 November 2005

38 In Russian: Mezhvedmostvennaya komissiya (межведомственная комиссия)

Ministry of Transports, Ministry of Atomic Energy, Ministry of Agriculture, FSB and the Federal Border Service.[39]

From the above, it is clear that Russia has thoroughly addressed the problem of bioterrorism in the past decade. Different types of measures have been taken on several levels and in various sectors of society. The measures are integrated in the existing systems for epidemiological control and biosecurity.[40] Part of this system and two major steps in counteracting bioterrorism are the two new centres in Sergiev Posad and Volgograd that are the focus of this study.

[39] The Working Group of the Federal Antiterrorist Committee on Questions of Protection of the Population, Agricultural Animals and Plants from Possible Application by Terrorists, Terrorist Groups or the Terrorist Organizations of Biological, Chemical and Other Agents of Mass Casualty, and also on Questions of Struggle against Illegal Circulation of Potentially Dangerous Agents and Materials; Ministry of Health, 'Order of 19 March 1999, No. 92, about a working group of the Federal Antiterrorist Committee', 19 March 1999

[40] Onishchenko, G.G. 'Bioterrorism counteractions: The strategy of the national health care', Vaktsinatsia, Vol. 21, No. 3 (May-June 2002)

Sergiev Posad Centres

The Virology Centre of the MoD Institute of Microbiology

The Virology Centre located in Sergiev Posad (formerly Zagorsk) is one of the facilities of the MoD Scientific Research Institute of Microbiology, which was the institute leading research and development of the military part of the Soviet offensive biological weapons programme. The Virology Centre was established in 1953 on the basis of the military Veterinary Microbiological Institute.[41, 42] As a part of the MoD Institute of Microbiology, the Virology Centre was subordinated to the 15th Directorate, which in turn was directly subordinated to the MoD in Soviet times. This directorate was responsible for the Soviet offensive biological weapons programme.[43] When the directorate was dissolved in 1992, the whole MoD Institute of Microbiology was transferred to the newly formed Radiological, Chemical and Biological (RCB) Defence Force, and sorts under the Force's Directorate for Biological Protection.[44]

Over the years, the Virology Centre has worked on a number of dangerous viruses with the aim to develop preventive and protective measures such as vaccines and antiviral preparations. According to the Russian CBMs of 1992, the MoD Institute of Microbiology developed "experimental forms of biological weapons agents" and tested them on animals.[45]

The Centre is reportedly divided into two zones called the "technical" and the "clean" zone, each with a guarded check-point, and the institute area is surrounded by a 2 metre concrete fence topped by four rows of barbed wire.[46] There are no research laboratories of the highest safety level (BSL-4)[47] but areas up to the safety level just below (BSL-3). The exact size has not been possible to determine, but these laboratories are part of the 6500 m^2 BSL-3 areas at the facilities in Sergiev Posad and Kirov of the MoD Institute of Microbiology.[48] The Virology Centre has apparently extensive animal facilities for mice, rats, rabbits, dogs, and monkeys. Notably these include high containment housing for horses used in Ebola experiments.[49]

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41 A. Rimmington. From Offence to Defence? Russia's Reform of its Biological Weapons Complex and the Implications for Western Security. The Journal of Slavic Military Studies, Volume 16, No. 1, March 2003, pp.1-43

42 John Hart. A historical note: The 50th anniversary of the founding of Russia's Virology Center at Sergiev Posad. ASA Newsletter, pp. 1,19-22, 28 February 2005

43 Joint Statement on Biological Weapons by the Governments of the United Kingdom, the United States and the Russian Federation (10-11 September 1992). Sipri, 10 September 1992, URL <http://projects.sipri.se/cbw/docs/cbw-trilateralagree.html>, accessed 9 June 2004

44 Orlov V.N. (ed.) My zashchitili Rossiyu [We Protected Russia]. Ministry of Defence, Moscow, 2000.

45 Russian Government. 1992. Information about facilities and biological activities of the Russian Federation, related to the Biological and Toxin Weapons Convention 1972, Confidence-Building Measure F 'Declaration of past activities in offensive and/or defensive biological research and development programmes'. 3 July, p.86.

46 Elena Mikhaylina. A feverish zone - the secrets of the numbered Zagorsks, Moskovskiy Komsomolets, 041208, URL <http://www.mk.ru/numbers/1406/article44343.htm>

47 According to the Western classification

48 Russian Government Information about facilities and biological activities of the Russian Federation, related to the Biological and Toxin Weapons Convention 1972, Confidence-Building Measures, 13 April 2005.

49 A. Rimmington. From Offence to Defence? Russia's Reform of its Biological Weapons Complex and the Implications for Western Security. The Journal of Slavic Military Studies, Volume 16, No. 1, March 2003, pp.1-43.

However, the animals are indicated to be bred elsewhere.[50] A strain collection of viruses is maintained at the Centre.[51] The hospital high-containment quarantine unit with 10-12 beds was originally created for the personnel.[52]

Since 1999, the Centre is headed by Vladimir Alekseevich Maksimov, Colonel of the Medical Services.[53]

The whole of the MoD Institute of Microbiology is closed to foreign visitors and foreign collaboration. In 2004, Maximov said that the Centre specialists have not worked with the WHO because the Centre has not received an invitation to do so. Once, the Centre donated 100 doses of Ebola immunoglobulin to the WHO for humanitarian use in Africa. Reportedly, it was a disappointment when the immunoglobulin was iverted to a US military research institute.[54]

The Virology Centre was included in the anti-terrorism and biosecurity Federal Target Programme"Zashchita" ("Protection").[55] Although this programme never may have been completely funded and implemented, the Centre was included in the intended programme activities, to produce large amounts of vaccines. The Centre was scheduled to receive a total of 20 million Roubles for reconstruction and modernisation of four buildings, but if these plans were realised is not known.

The Virology Centre was the foremost research institute on viruses in the USSR until Vector was created in 1974 as part of the "civilian" branch of the BW programme. It is assessed to have kept its unique position within the military funded biological research programme. Being the main military facility for research on defence against viruses, it has been given unique resources that are reflected in its research achievements and level of competence, described in the next section.

Areas of competences of the Virology Center

The MoD Center of Virology of the Institute of Microbiology is well suited for hosting the Centre of Special Laboratory Diagnostics and Treatment of Especially Dangerous and Exotic Infectious Diseases (CSDT). The scientists of the virology centre have for decades worked with questions concerning protection to biological warfare agents with focus on viral and rickettsial agents. It is likely that the widening of focus from defence to BW agents to measures against bioterrorism has been easily carried out. An evaluation and categorisation of pathogens of especially dangerous infections was presented in 1999 by scientists of the

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50 Elena Mikhaylina. A feverish zone - the secrets of the numbered Zagorsks, Moskovskiy Komsomolets, 12 August 2004, URL <http://www.mk.ru/numbers/1406/article44343.htm>

51 Markin, V.A., et al., 1996.

52 Lukina RN, Lukin EP, Bulavko VK (eds.). Dostiyny izvestnosti [Deserving Fame]"; 50th anniversary of the Virology Centre of the MoD. Council of Veterans at the Virology Centre of the MoD, 10 January 2004.

53 Fedor Smirnov. Dangerous viruses: A center for the diagnostics and treatment of exotic and dangerous infectious diseases. ASA Newsletter, No. 00-1, pp. 9-10, 2000, 29 February 2000.

54 Udmantsev V. Russian Military Microbiology - Ministry of Defence Virology Centre turned 50. Voenno-Promyshlenniy Kuryer, No. 16 (33), 28 April - 11 May 2004, URL <http://www.vpk-news.ru/article.asp?pr_sign=archive.2004.33.articles.rostrum_01>, accessed 3 May 2004

55 Cf. footnote 31.

centre.[56] This categorisation is remarkably similar to a rating list of BW agent candidates published by Vorobev, former deputy director of science at the Centre (Appendix A).[57,58]

Publications are presumed to provide a common view of the competence and the research of an institute. With the purpose to make a brief assessment of the areas of competences of the Virology Center, a review of the publications from the last two decades (1985-2004) has been performed.[59] In addition to publications in scientific journals, abstracts from a scientific symposium organised by the MoD Institute of Microbiology have been reviewed. The referred publications are found in Appendix B.

Table 1. Organisms in research focus of the Virology Center

Organism	**Organism name in titles of publications 1985-1994 (43)**	**Organism name in titles of publications 1995-2004 (38)**	**Organism on priority lists[58]**
Encephalitis viruses VEE, EEE, TBE	11	2	Yes, No. 5
Congo-Crimean/Omsk HF virus	2	1	No
Ebola virus	3	6	No
Ehrlichia and Bartonella	-	1	No
West Nile fever and Hantaan virus	-	2	No
Lassa and Machupo fever virus	5	3	No
Marburg virus	3	2	Yes, No. 8
Orthopoxviruses	2	4	Yes, Variola is highly scored (No. 1)
Rickettsia and Coxiella	5	7	Yes, Coxiella is highly scored (No. 7)
Rift Valley fever virus	1	-	No

It is concluded from this brief comparison that the focus of research is relatively static. Almost the same organisms dominate in the period 1985-1994 as in 1995-2004. The main difference between the two time periods is the number of publications on arboviruses; a reduction from 11 to 2 papers. There is also a doubling of the number of publications on Ebola virus. In the period 1995-2004 five new names of organisms – *Ehrlichia*, *Bartonella*, Hantaan virus, West Nile fever virus and Machupo virus – appear in single studies, while a

[56] Chebotarev, E.V., et al., 1999.

[57] Vorobev, A.A. 2001.

[58] Kondrik et al., 2003.

[59] These publications, of which the affiliation of the first author is the Virology Center, were found in the two literature data bases Biosis and MedLine.

study on the Rift Valley fever virus is only reported in the former period. The list of viruses which have been in focus were compared with a rating list of bioagents based on a system developed by domestic scientists.[60] Four virus or virus groups of the priority lists are found among the reviewed publications of the Center of Virology, see Table 1. Six of the virus groups studied are not classified as prioritised organisms according to the rating list. All the reviewed papers were published in Russian journals. No paper in English has been found.

The publications reflect that the efforts have been spent on developing means of identification and treatment of the infectious agents as well as vaccine development. In some of the seven publications in 1985-1989 the development of a typhus vaccine strain (*Rickettsia prowazekii*) is the main topic. Other papers reflect an interest in the role of interferon in viral infections and also as inducer of the immunogenicity of vaccines. Antiviral drugs were on the agenda in this period and the inhibitory effect of drugs on cell culture proliferation was evaluated. Apart from the typhus bacterium (Rickettsia) there is no specific focus of organisms in the titles of the publications.

In the first five years of the 1990s there was a dramatic increase in the number of publications. The 36 papers which have been reviewed represent a concern in antiviral agents and means of delivery of drugs and antibodies to infected individuals, design of vaccine strains, and the development of animal systems for tests of vaccines. The prospect for using viruses as vaccine vectors was discussed. In the period there was a growing interest in the construction of recombinant vaccine strains. Questions concerning pathogenesis and transmission were studied in animal systems. Another apparent interest according to the reviewed papers was to maintain the properties of viral strains in efficient cell culture propagation. In addition, other aspects of production problems such as concentration and purification of antigens, and storage, were studied. A strong focus on the encephalitis viruses was observed and the Venezuelan equine encephalitis virus was the agent of choice in one fourth of the papers. In addition, the Ebola, Marburg and Lassa fever viruses were frequently found in the publications of this five year period. Rickettsia species were also in focus.

In the latter part of the 1990s the publication frequency decreased and only 20 papers were available for reviewing. The continuous interest in exotic viruses was apparent and it was mainly focused on the Ebola, Marburg, Lassa and VEE virus. Other viruses of interest were the orthopoxviruses[61]. Some of the publications dealt with rickettsial agents. The publications reflected new findings in the struggle to develop vaccines and treatments of acute infections caused by these infectious agents. Treatment of VEE as well as Ebola and Lassa fever was of high interest and methods for the identification of the VEE and Ebola viruses were published.

An additional 24 papers from a symposium organised by the Institute of Microbiology in 1999 were also reviewed.[62] These papers were mainly focused on the development of vaccines and on questions concerning propagation of viruses. In addition, issues concerning treatment of virus infections were discussed. There were also some papers discussing methods

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60 Vorobev, A.A. 2001. Evaluation of probability of use of bioagents as biological weapons. Epidemiol. Infect. Dis. No. 6, 54-56. See Appendix A.

61 The orthopoxvirus group comprises for instance the Vaccinia, camelpox, monkeypox and Variola viruses.

62 These papers from the Scientific Conference to the 50th Anniversary of the MoD Centre for Military-Technical Problems ”Diagnostics, Treatment and Prophylaxis of Infectious Diseases. Biotechnology. Veterinary Medicine.” (Ekaterinburg, Russia.) are included in Appendix B.

for sampling of aerosol particles and assessment of aerosol composition. A categorical list of pathogens of especially dangerous infections was presented at the symposium.

The 18 papers in the first period of the new millennium reflected a general concern in safety of vaccines and surprisingly, in smallpox vaccinations (smallpox is an eradicated disease which has been re-assessed as a threat from bioterrorism). The epidemiology and possible treatment of Omsk and Congo-Crimean hemorrhagic fever viruses were also studied. New names of viral agents appeared in the papers, for instance prophylaxis to the West Nile and Hantaan viruses. These viruses reflect a wider interest in agents which have been reported in recent outbreaks in the West.

The affiliations of the authors of the publications reflect that the scientists of the Center of Virology have an extensive net of contacts by collaboration with various research institutes in the Russian Federation:

The Research Institute of Plague Control (Anti-Plague Institute) in Stavropol and Rostov

The Ivanovsky Institute of Virology in Moscow

The Institute of Molecular Biology NPO “Vektor” in Koltsovo

The State Institute of Physico-Chemical Medicine in Moscow

The Institute of Pharmacology of the Tomsk Scientific Center in Tomsk

The Design-Technological Institute of Biological Active Compounds Vector in Berdsk

The Sechenov Moscow Medical Academy in Moscow

The Gamaleya Research Institute of Epidemiology and Microbiology in Moscow

The Tarasevich State Research Institute for Standardization and Control of Modern Biological Preparations in Moscow

The State Medical Academy in Perm

The Shemyakin-Ovchinnikov Institute of Bioorganic Chemistry in Moscow

The affiliations of the co-authors also indicate cooperation with the Botkin State Clinical Hospital in Moscow. In addition to these research establishments, cooperation with the other institutes subordinated to MoD is expected.

In the section below the published research is presented as areas of competences.

Epidemiology

Mathematical modelling has been developed as a mean to assess the risk for epidemic out-breaks in the Russian Federation. The risk for development of epidemic louse-borne typhus was, for instance, calculated based on the national situation and the number of possible sources.[63] It was emphasised that the modern databases make it possible to predict the epi-demic process for this agent as well as other rickettsial agents.[64] In addition to *Rickettsia,* the epidemic situation concerning viral hemorrhagic fevers was assessed.[65] Based on the epi-demic situation in Russia, advices concerning the requirement for immunisation and means of treatment for rickettsial infections have been formed. It was concluded that a low incidence rate of rickettsial diseases in combination with access to effective therapy in Russia limit the

63 Lukin, E.P., et al., 1996.

64 Lukin, E.P., and Iu.V. Nesvizhskii, 2003.

65 Markin, V.A., and V.I. Markov, 2002.

need of vaccination to high-risk groups. Moreover, vaccination was found to be necessary only for three rickettsial diseases - typhus, Rocky Mountain spotted fever and Q fever.

The studies have also been focused on ecological aspects of zoonotical[66] pathogens such as *Ehrlichia*, *Bartonella* and *Rickettsia prowazekii*.[67, 68] Data has been presented on the natural circulation of *Bartonella* and *Ehrlichia* with the participation of lice, fleas, mosquitoes, Ixodes ticks as well as rodents, larger wild animals and domestic animals.

Modern molecular and genetic analyses of micro-organisms are more adequate methods than those previously used for identification and search of source of agent. It was stressed that the improvement of methods for taxonomy and classification, for instance of *Rickettsiae*, has generated considerable changes in the conventional scheme of handling an infection.[69]

The Center of Virology has set up and is maintaining a strain collection of pathogenic viruses.[70] One of the main requirements in maintaining such a collection is to take measure to preserve the original properties of each strain. A universal research programme for the creation of a specialised National Museums of Pathogens within the framework of the Russian State Collection of Microorganisms has been proposed. It was emphasised that the organisation and methodology should be separate concerns while working with strain collections.

Growth of viruses in various systems

Much emphasis has been focused on the development of methods for propagation of viruses – pathogens as well as attenuated vaccine strains - in cell cultures and in this work the selection of the optimal host cell line was crucial. Work has been performed both on cell tissue cultures and suspension cultures[71,72] Efficient propagation of viruses in suspension cultures in fermenters was concluded to require microcarriers. The composition and pH of the cell culture media for suspension cultures were critical tested in order to find the most efficient conditions for various virus strains. The most appropriate cell lines were selected by testing the sensitivity of the cells for various virus strains as well as the level of accumulated viruses.[73, 74] The scientists were successful in developing systems for the viruses of interest. In 2002 it was, for instance, reported that the culturing properties and sensitivity to the Ebola virus were retained by cell propagation during 5.5 months (24 passages) of growth on microcarriers in a fermenter suspension.

The effect of long-term storage on the stability of cell lines, which have been selected for continuous growth of viruses, was also of concern and transformed cells were carefully characterised after years of storage.[75]

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66 Infection is transferred from animals to humans.

67 Lukin, E.P., and P.A. Grabarev, 1999.

68 Grabarev, P.A., et al., 1998.

69 Lukin, E.P., A.A. Vorob´ev, and A.S. Bykov, 2001.

70 Markin, V.A., et al., 1996.

71 Pashchenko, Yu.I., V.F. Prokhor, and I.V. Borisevich, 2002.

72 Krotkov, V.T., 1999.

73 Krotkov, V.T., et al., 1999.

74 Pashchenko, Yu.I., V.F. Prokhor, and I.V. Borisevich, 2002.

75 Lymar', V.T., et al., 1992.

The stability of the viral properties has been a question of concern for the scientists at the Center of Virology. For instance, the effect of the culturing system on the phenotypic resistance of the VEE virus was determined.[76] In order to find a simple way to preserve the original properties of each virus strain the possibility of using ticks as hosts in research was investigated. The risk for genetic drift, i.e. the frequency of random changes in the genome, is enhanced by each passage on laboratory model systems such as cell tissue cultures. Experiments with the CCHF virus showed that optimal propagation with retained clinical effect was obtained by alternating the propagation of virus in cells and in natural carrier organisms or animals. It was for instance described that alternative passages in mice as well as in the tick *Alveonasus lahorensis* restored the pathogenicity of the virus.[77]

Animal model systems

The interaction between various viruses and hosts were studied in animals such as monkeys, guinea pigs and mice. It is noticeable that monkeys have frequently been used. Monkeys are more expensive and they also require much more space than experiments with rodents. Statistical aspects on experimental viral infections were elaborated and for each infectious agent, for instance the Marburg fever virus, the sensitivity of various animals was evaluated.[78,79] Moreover, the ways of transmission of viruses between individuals were studied in animals, such as monkeys, experimentally infected by the Marburg virus.[80] The animals were exposed to the agents by aerosol or by injection and various aspects of viral infections were taken into consideration.[81] When Lassa fever was experimentally induced in baboons by intramuscular inoculation and by aerosol exposure, the clinical symptoms observed resemble those reported in human infections.[82] By the use of discriminatory analysis and informative markers of disease it was possible to differentiate between pathogenic strains of VEE virus in experimentally infected baboons.[83] When guinea pigs were used as animal model system to study the pathogenesis of the Q fever agent *Coxiella burnetii*, it was possible also to differentiate between virulent strains.[84]

The effects of antiviral agents were tested in experimental infected animals, see further the section Treatment. Animal model systems were also used for the evaluation of various vaccines, which is described in the following part.

Vaccine development

The Center of Virology has a long history of the development of live virus and bacteria vaccines. For instance, vaccines to various well-known diseases such as plague, tularemia, yellow fever, epidemic typhus and Q fever have been developed. Live inactivated or attenuated organisms were constructed to be used in vaccines. Studies have shown that these vaccines in general are safe and stable. It was for example shown in the 1990s that a live virus vaccine

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76 Khamitov, R.A., et al., 1996.

77 Ionov, S.N., et al., 1999b.

78 Ionov, S.N., S.L. Kirillov, and V.A. Pshenichnov, 1990.

79 Gonchar, N.I., et al., 1991.

80 Pokhodiaev, V.A., N.I. Gonchar, and V.A. Pshenichnov, 1991.

81 Ionov, S.N., S.L. Kirillova, and V.A. Pshenichnov, 1990.

82 Evseev, A.A., et al., 1991.

83 Khamitova, R.A., V.B. Kirillov, and G.G. Khaltaeva, 1999.

84 Suvorova, T.A., V.A. Pshenichnov, and P.A. Grabarev, 1991;1997.

(VEE) from the 1960s, frequently used for field trials and vaccination of researchers, had retained its properties.[85]

For a successful vaccine development the test of the various vaccine candidates in suitable animal models is required. For instance, hamadryas baboons were used in studies of vaccine against Ebola fever, guinea pigs for the assessment of the efficacy of a vaccine against Lassa fever and white rats in tests of VEE vaccine.[86, 87, 88]

The study of virulence factors and immunogenic components of an infectious agent generates a crucial knowledge in vaccine development. Many of the publications of the centre reflect an interest in viral immunogenic proteins and the antibodies directed to these antigens.[89, 90, 91, 92] Methods have been developed for concentration and purification of antigens for use in vaccines, for instance a chemical dry typhus vaccine.[93] Polyclonal serum and monoclonal antibodies[94] directed to crucial antigens were useful tools in the studies. Moreover, serum and antibodies are practical for the development of immunological identification methods and also for prophylaxis and acute treatment of individuals exposed for viral agents, for instance after a laboratory incidence. The effectiveness of virus-specific proteins in immunologic processes was studied during experimental Marburg fever and monoclonal antibodies were directed to a structural glycoprotein of the Marburg fever virus.[95] Hybridoma cells producing monoclonal antibodies to Ebola virus were also constructed.[96]

The acquired knowledge has been used for the development of vaccines to infections caused by encephalitis and hemorrhagic viruses such as the VEE, TBE and Lassa fever virus.[97, 98, 99, 100] An attenuated VEE strain was found to be efficient in immunization of rodents and monkeys even at low doses.[101] It provided protection against respiratory challenge with a wide range of doses of highly virulent VEE virus strains. In the vaccination experiments with the attenuated VEE virus strain it was found that white mice and Syrian hamsters also had obtained a partial immunity to intra-nasally exposure of the related Eastern

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85 Lukin, E.P., A.A. Makhlay, and N.K. Chernikova, 1999.

86 Firsova, I.V. et al., 2003.

87 Mikhailov, V.V., et al., 1994a.

88 Moshkov, S.P., et al., 1991.

89 Donchenko, V.V., et al., 1996.

90 Borisevich, I.V., et al., 1995; 2003.

91 Ruchko, S.V. et al., 2001.

92 Krasnianski, V.P. et al., 1994b; 1997.

93 Khamitov, R.A., et al., 1999b.

94 A polyclonal serum is obtained by immunisation of animals and it contains a mixture of antibodies directed to various antigenic determinants. Monoclonal antibodies are produced by hybridoma technology and originate from a single clone, i.e. they are identical.

95 Donchenko, V.V., et al., 1996.

96 Pashchenko, Yu.I., et al., 1999.

97 Pshenichnov, V.A., et al., 1991.

98 Krasnianskii, V.P., et al., 1993.

99 Evstigneev, O.V., et al., 1999.

100 Krasnianskii, V.P., et al., 1994b.

101 Filatenkov, A.G., et al., 1991a,b.

equine encephalitis virus (EEE).[102] The animals resisted low doses of EEE, while higher doses led to an established infection.

Modern genetic techniques for the creation of new vaccines were considered.[103] In recent years genetic methods have been used to construct recombinant vaccine strains which express components from various viral and bacterial strains. For instance, vaccines were constructed against tick-borne encephalitis based on the recombinant viral strain “Revaks-TBE” expressing TBE virus proteins and against Venezuelan equine encephalitis based on the vaccine strain VR26S with structural genes from the VEE virus.[104] The culturing of recombinant virus vaccine strains in cells has been emphasised.[105]

Much emphasis seems to have been focused on the development of oral vaccines. The administration of the vaccines was tested in mice, guinea pigs, rabbits and monkeys.[106] Several publications reflect a genuine belief in the advantage of oral vaccines and, for instance, oral immunisation to smallpox was investigated.[107, 108, 109, 110, 111] A comparison between oral and epicutaneous immunisation against smallpox showed that oral immunisation with vaccinia was safe and effective.[112]

The successful preparation of tablets containing vaccine to several viral diseases, including VEE, TBE and swine pest virus, has been performed.[113]

A previously developed dry live enteral vaccine to Q feber was found not to have enough specific activity. In order to improve the vaccine, a vaccine in tablet form was produced and tested in guinea pigs and monkeys.[114]

It was concluded that peroral vaccines - in contrast to conventional injected vaccines -may well be produced in transformed cell lines using modern industrial cell technology. The peroral preparations require less stringent production, i.e. a limited amount of apatogenic microorganisms and heterogenic DNA and protein are allowed.[115]

Special emphasis is given to the safety of vaccines[116, 117] This includes the risk for residual virulence of live virus vaccine strains. Methods to test the properties of various vaccine sub-

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102 Filatenkov, A.G., 1991c.

103 Ruchko, V.M., et al., 2002.

104 Evstigneev, O.V., et al., 1999.

105 Krotkov, V.T., 1999.

106 Makhlai, A.A., et al., 1997.

107 Podkuyko, V.N., et al., 1999a,b.

108 Podkuyko, V.N., and A.A. Vorobev. 1999a,b.

109 Podkuiko, V.N., et al. 1993.

110 Vorob'ev, A.A., V.N. Pudkuiko, and V.V. Mikhailov, 2002.

111 Vorob'ev, A.A., V.N. Pudkuiko, and V.A. Maksimov, 2003.

112 Bektimorov, T.A. et al., 2002.

113 Borisevich, I.V., et al., 1999.

114 Mikhailov, V.V., et al., 1996; 1999.

115 Podkuyko, V.N., et al., 1999a.

116 Makhlai, A.A., et al., 1999.

117 Mikhailov, V.V., et al., 1994b.

strains have been developed in order to evaluate the immunogenicity and residual virulence.[118, 119, 120] When smallpox vaccination among children resulted in iatrogenic vaccinia, scientists from the Center collaborated in isolation, identification and characterisation of the causative virus.[121]

In the recent period the development of new generations of vaccines has been discussed, for instance the use of molecular genetical techniques for the construction of DNA vaccines, transgenic and anti-idiotypic vaccines and recombinant virus vectors.[122, 123, 124, 125] According to the publications, the prospects for using RNA viruses as vectors were first suggested by the scientists at the Virology Centre in the beginning of the 1990s.

Treatment

In addition to vaccine development, the main interest of the institute is stated to be means for "treatment of highly dangerous and exotic infectious diseases". Various antiviral agents such as ribamidil, virazole, realdir and amixin were evaluated in animals experimentally infected by Lassa virus, OHF virus, Hantaan virus, VEE virus and West Nile fever virus.[126, 127, 128, 129, 130]

Liposomes were developed for use as carriers of antiviral agents and for instance ribamidil-containing liposomes were reported to be efficient in experimental Rift Valley fever.[131, 132, 133] The effect of antiviral agents was evaluated also in cell tissue cultures.[134, 135]

The antiviral chemotherapeutic substance amixin used in the experiments with Hantaan, West Nile fever and OHF virus is an interferon-inducing agent. The idea was to induce the host´s own production of interferon, which would have an antiviral activity. In addition to the direct or indirect antiviral efficiency of chemotherapeutic agents, the antiviral effect of interferon

118 Pshenichnov, V.A., et al., 1985.

119 Khamitov, R.A. V.A. Pshenichov, and P.A. Grabarev, 1985

120 Pshenichnov, V.A., et al., 1988.

121 Onishchenko, G.G., V.I. Markov, V.N. Ustiushin, S.V. Borisevich, G.I. Kuznetsova, S.Ia. Loginova, A-M. Berezhnoi, N.T. Vasil´ev, V.A. Maksimov, A.A. Makhlai. 2001. Isolation and identification of the smallpox virus which caused iatrogenic vaccine in children in the city of Vladivostok. Zh. Mikrobiol. Epidemiol. Immunobiol. No. 2, 40-45.

122 Ruchko, V.M., et al., 2002.

123 Ruchko, V.M., et al., 1999.

124 Mikhailov V.V., V.M. Ruchko, and A.A. Makhlai, 2001.

125 Moshkov, A.E., et al., 1993.

126 Dvoretskaia, V.I., et al., 1990; 1991.

127 Loginova, S.Ia., et al., 2002a.

128 Loginova, S.Ia., et al., 2002b.

129 Loginova, S.Ia. et al., 2004.

130 Markin, V.A., R.M. Mustafin and V.A. Pshenichnov, 1991.

131 Pshenichnov, V.A., R.A. Khamitov, and A.V. Koloskov, 1990.

132 Khamitov, R.A., et al., 1993.

133 Grabareva, L.P., R.A. Khamitov, and V.A. Pshenichnov, 1991.

134 Lymar´, V.T., and A.V. Pshenichnov, 1988.

135 Pshenichnov, A.V., V.A. Konyukhov, and V.T. Lymar', 1989a.

preparations was evaluated.[136] The effect of interferon in primates infected with orthopoxvirus was studied.[137] In parallel experiments, animals were injected with recombinant alpha-2-interferon and the accumulation of the cytokine was compared with that of interferon induced by the addition of larifan and rifastin, respectively.

The use of antiserum (immunoglobulins) is a mean for acute treatment as well as prophylaxis of viral diseases. Hyper-immune sera were produced against Ebola and Lassa fever viruses.[138] The use of liposomes for delivery of immunoglobulins was taken into consideration, for instance for treatment of Marburg fever.[139]

As mentioned previously the scientists of the Virology Center also developed hybridomas producing monoclonal antibodies (Mab) directed to components of various viruses. One of the more successful research lines seems to have been Mab directed to the Ebola virus.[140] In 1997 it was concluded that the "therapy of Ebola fever should be based on the earliest possible and sufficiently prolonged administration of specific immunoglobulins in combination with pathogenic drugs".[141] Furthermore, in a review of the literature published in 2000 it was concluded that it is reasonable to direct the development of therapeutic strategies to optimal combinations of unspecific and immunobiological drugs with symptomatic medical treatment.[142]

The technique to prepare fragments of immunoglobulins (FAB) has been used. The efficiency of such FAB-fragments against experimental VEE infections in rabbits was evaluated.[143] In addition to antibodies, antibody fragments and monoclonal antibodies, anti-idiotypic antibodies[144] have been developed.[145] Attention was paid to the immunomodulatory effect of antiidiotypic antibodies directed to VEE virus.

Methods to evaluate the sensitivity of *Rickettsia* to anti-bacterial agents (chemopreparations) have been published.[146] These methods involve both *in vitro* (by the inhibition of hemolytic activity) and *in vivo* (under the conditions of experimental pulmonary rickettsiosis in mice), with the use of the rapid method for the determination of the number of metabolically active *R. prowazekii*.

Recent publications reflect the interest in modern technology for production of medical preparations in recombinant systems.[147, 148] The use of transgenic plants for production of antigens,

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136 Pshenichnov, V.A., and Iu.N. Malinkin, 1988.

137 Loginova, S.Ia., et al., 1997.

138 Krasnianskii, V.P., et al., 1994a; 1995; 1997.

139 Khamitov, R.A. et al., 1999a.

140 Pashchenko, Yu.I. et al., 1999.

141 Markin, V.A., et al., 1997.

142 Markin, V.A., 2000.

143 Ionov, S.N., et al., 1999a.

144 An antiidiotypic antibody which is directed to another antibody and binds to it, may mimic antigenic determinants recognised by the original antibody, i.e. to serve as a surrogate antigen.

145 Markov, V.I., V.A. Pschenichnov, and A.A. Makhlay, 1993.

146 Predtechenskii, A.B., and G.N. Filipenko, 1997.

147 Ruchko, V.M., et al., 1999.

148 Mikhailov V.V., V.M. Ruchko, and A.A. Makhlai, 2001.

antibodies, enzymes and hormones has been reviewed and it is concluded that transgenic plants are effective for the production of bioactive molecules. The technology developed for medical preparations in powder form was concluded to be optimal from mass and energy saving view.[149] The use in vaccines of viral and bacterial antigens, which have been expressed in transgenic plants, was emphasised.

An area of interest seems to be the development of concepts for safe and efficient storage and transport of thermo-labile biological preparations such as vaccines and antibodies.[150]

The know-how in preparation of material in powder form and of an optimal particle size (<15 µm) was reflected in one publication.[151] The method was applied on mixtures of dried and liquid substances, including thermo-labile substances, for medical preparations. Specific additives were used in order to avoid aggregate formation.

Identification methods

According to the publication list, methods for identification of viruses have been one of the concerns of the Virology Centre. The methods include those with immunological as well as genetic basis. For instance, in the 1990s immunoassays were developed for Marburg, Ebola, VEE and orthopoxviruses, including Variola.[152, 153, 154, 155]

The use of genetic methods was reported in the 1990s, for instance the identification of the encephalitis virus causing VEE and EEE as well as various alphaviruses.[156] Later a PCR-based method for the hemorrhagic fever viruses causing Marburg and Ebola fever was published.[157] Initially, an algorithm for the search of genetic determinants for RNA viruses was developed. By computer analysis of the nucleotides in the genome of Ebola and Marburg virus highly specific primers were possible to construct. A solid phase synthetic method for primers was developed.

Aerosol techniques

Research has been performed on the dispersion of an aerobiosystem at the Virology Center.[158] Mathematic models to describe the movement of aerosol particles and an experimental system for control of the theoretical model as well as methods to roughly determine particle sizes were developed. In addition, means to determine the basic properties of an aerobiosystem was developed, for instance a procedure for sampling and assessment of the dispersion composition of biological aerosols at static conditions.[159] Other parameters of interest in the research have been the physical stability of the aerosol particles and their biological properties.

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149 Vlasov, N.G., et al., 1999.

150 Ogorodnikov, A.I., et al., 1999.

151 Vlasov, N.G., et al., 1999.

152 Vinskaia, A.I., and Yu.Yu. Grigorashkin, 1992.

153 Kutuzov, V.A., et al., 1993.

154 Gradoboev, V.N., et al., 1996.

155 Borisevich, I.V., et al., 1996.

156 Vinskaya, A.I., et al., 1992.

157 Merkulov, V.A., et al., 1999.

158 Solyakov, I.Yu., and A.G. Osipov, 1999.

159 Gorskiy, V.V., A.G. Osipov, 1999.

The Centre of Special Laboratory Diagnostics and Treatment of Especially Dangerous and Exotic Infectious Diseases

The Centre of Special Laboratory Diagnostics and Treatment of Especially Dangerous and Exotic Infections (CSDT) was created as an alternative to a national network of many and much smaller centres with the same functions in countering bioterrorism.[160] The idea of this centre was supported by Gen. Stanislav Petrov, then head of the Radiological, Chemical and Biological (RCB) Defence Force, and Lt.-Gen.Valentin Yevstigneev, head of the Directorate for Biological Protection of the Force.[161] The CSDT is a joint MoD and MoH organisation and was established by a joint decree on 20 Nov. 1999 (Appendix C)[162] and located at the MoD Virology Centre in Sergiev Posad.

The MoD, through the Virology Centre, is responsible for "maintaining a laboratory base, staff and services assuring permanent preparedness to carry out laboratory diagnostics, and also for receiving persons, under surveillance for infectious pathogens of especially dangerous and exotic infectious diseases, for hospitalisation and treatment" and also the "maintenance of a stockpile of diagnostics, immunobiological and medical materials". The head of the Virology Centre also heads the CSDT and appoints the employees of the Virology Centre that work at the CSDT. Other resources utilized by the CSDT are the strain collection of viruses at the Virology Centre to which the CSDT is tasked with adding more samples. In addition, the hospital high-containment of the unit of the Virology Centre can be used by the CSDT for observation and treatment.

The MoH is tasked with placing at the disposal of the CSDT, epidemiological data (e.g. incidence at natural foci) on especially dangerous and exotic pathogens, and clinical-epidemiological information for directing probes for analysis or persons for hospitalisation, as well as the required equipment, reagents, immunobiological preparations and medical materials for the CSDT. Specialists of the MoH can also be consulted in the hospital care for infected persons.

The ultimate responsibility for the CSDT lies with the First Deputy Minister of Defence (who is also responsible for the RCB Defence Force), and the First Deputy Minister of Health (also Sanitary Surgeon General). The mechanisms of authorisation are very detailed in the decree, involving the First Deputy Minister of Health and the Head of the RCB Defence Force.[163]

According to the decree the tasks of the CSDT are:[164]

- "Performing laboratory diagnostics on various pathogens of especially dangerous and exotic infections, or antibodies against these;

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160 Onishchenko GG, Vasil'ev NT, Maksimov VA, Markov VI, Borisevich IV, Fedorov IuM. Center of special laboratory diagnostics and treatment of dangerous and exotic infectious diseases in the system of the antiepidemic protection of the territory of the Russian Federation. Zh Mikrobiol, Epidemiol Immunobiol. 2001 November-December; (6):114-5, 2001.

161 Fedor Smirnov. Dangerous viruses: A center for the diagnostics and treatment of exotic and dangerous infectious diseases. ASA Newsletter, No. 00-1, pp. 9-10, 29 February 2000.

162 Order No. 558 of the MoD and No. 416 of the MoH about a Centre of Special Diagnostics and Treatment of Especially Dangerous and Exotic Infectious Diseases, 20 Nov. 1999.

163 Cf. Appendix C.

164 The full text of the decree is found in Appendix C.

- Isolation of pathogens from samples, their subsequent identification, preservation and deposition;
- Hospitalisation and treatment of patients with (or persons under observation for) especially dangerous and exotic infections until diagnostically disease-free;
- Development and creation of mock samples, containing pathogens of especially dangerous and exotic infections, for the evaluation of the efficiency of measures to assure the sanitary-epidemiological status of the territory of the RF;
- Development of proposals for performing special laboratory diagnostics, introducing new materials and methods and their utilisation, and improving the systems of prevention and liquidation of the consequences of entry and spread of especially dangerous and exotic infectious diseases on the territory of the RF."

The CSDT has carried out several of its specified tasks since the start in 1999. Samples from eight outbreaks and a total of over 500 samples were analysed in the first two years, and after four years the CSDT had analysed over 600 samples both from humans and animals.[165, 166] Between May and November 2005, over 200 samples from 12 oblasts and krais related to avian influenza were analysed by the specialists of the RCB Defence Force.[167] Many samples reach the CSDT from other facilities all over Russia that perform the actual sampling, but the CSDT also has a mobile team "equipped with everything necessary for taking samples from infected persons and environmental objects" and that can carry out analyses on the spot.[168]

Four of the outbreaks that the CSDT participated in investigating are:

- Congo-Crimean hemorrhagic fever outbreak in Stavropol krai, 1999. The CSDT had not been offically established by order, but staff from the Virology Centre traveled to the site(s) of the outbreak assisting the sanitary-epidemiological establishment.[169] When Maksimov describes the activities of the CSDT he includes also this outbreak.[170]
- Accidental vaccinia infection in Vladivostok, 2000. In a research article submitted October 2000, the CSDT reported its investigation of the accidental cases of vaccinia infection in Vladivostok that occurred June 2000[171]. Samples from all the eight

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165 Onishchenko, G.G., N.T. Vasil'ev, V.A. Maksimov, V.I. Markov, I.V. Borisevich, Iu.M. Fedorov. 2001. Center of special laboratory diagnostics and treatment of dangerous and exotic infectious diseases in the system of the antiepidemic protection of the territory of the Russian Federation. Zh. Mikrobiol. Epidemiol. Immunobiol. No. 6, 114-115.

166 Udmantsev, V. Russian Military Microbiology - Ministry of Defence Virology Centre turned 50. Voenno-Promyshlenniy Kuryer, No. 16 (33) 28 April - 11 May 2004, 28 April 2004, URL <http://www.vpk-news.ru/article.asp?pr_sign=archive.2004.33.articles.rostrum_01>, accessed 3 May 2004.

167 Sergey Severinov. There are special demands on us. Krasnaya Zvezda, 11 November 2005, URL <http://www.redstar.ru/2005/11/12_11/2_02.html>, accessed 16 November 2005.

168 Onishchenko, G.G., N.T. Vasil'ev, V.A. Maksimov, V.I. Markov, I.V. Borisevich, Iu.M. Fedorov. 2001. Center of special laboratory diagnostics and treatment of dangerous and exotic infectious diseases in the system of the antiepidemic protection of the territory of the Russian Federation. Zh. Mikrobiol. Epidemiol. Immunobiol. No. 6, 114-115.

169 Fedor Smirnov. Dangerous viruses: A center for the diagnostics and treatment of exotic and dangerous infectious diseases. ASA Newsletter, No. 00-1, pp. 9-10, 2000, 29 February 2000.

170 Udmantsev, V. Russian Military Microbiology - Ministry of Defence Virology Centre turned 50. Voenno-Promyshlenniy Kuryer, No. 16 (33) 28 April - 11 May 2004, 28 April 2004, URL <http://www.vpk-news.ru/article.asp?pr_sign=archive.2004.33.articles.rostrum_01>, accessed 3 May 2004.

171 Who criticizes Russia for handling of smallpox virus. RFE/RL, , 20 June 2000

infected children were studied. The experiments included PCR amplification by a method developed at the Virology Centre, and restriction fragment length analysis to compare to the vaccine preparation. Comparisons were also made to cultured rabbit, buffalo and monkey pox virus although the latter is not reported in detail.[172]

- SARS, 2003. In addition to sampling, detection and identification, the CSDT has partially characterised a corona virus strain ”CoD” from a Russian SARS patient and deposited the strain in the collection of the Virology Centre.[173] This in turn led to the development of a SARS detection method for routine use, in collaboration with the Saratov Anti-plague Institute ”Mikrob”.[174]
- Avian influenza, 2005. The avian influenza epidemic is taken seriously in Russia that has extensive borders to Asian countries and suffered many cases in wild birds. Among the experts that discussed the threat from this disease in Oct. 2005 was staff from the MoD Institute of Microbiology.[175]

The CSDT has participated in writing more than 10 normative documents, in line with the tasks listed in the order establishing the CSDT.[176] Giving lectures for experts of the Federal Sanitary-Epidemiological Monitoring Service is not explicitly mentioned in the decree for the CSDT, but Maksimov lists this among the centre’s activities.

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172 Onishchenko, G G, Markov, V I, Ustyushin, V N, Borisevich, S V, Kuznetsova, G I, Loginova, S N, Berezhnoi, A M, Vasilyev, N T, Maksimov, V A, Makhlai, A A. 2001. Isolation and identification of smallpox vaccine virus which caused iatrogenic vaccinia in children in Vladivostok. Zh. Mikrobiol. Epidemiol. Immunobiol. No. 2, 40-45

173 Onishchenko, G.G., N.T. Vasil'ev, V.A. Maksimov, V.I. Markov, V.A. Merkulov, M.N. Pistsov, A.M. Berezhnoi, S.I. Syromiatnikova, V.V. Zubov. 2003. Isolation and identification of the infective agent of severe acute respiratory syndrome (SARS) from a patient with atypical pneumonia. Zh. Mikrobiol. Epidemiol. Immunobiol. No.5, 109-112

174 Boris Talov. Atypical pneumonia declassifies our military. Rossiyskaya Gazeta, 30 August 2003, URL <http://www.rg.ru/Anons/arc_2003/0830/3.shtm>, accessed 18 March 2004.

175 Maxim Bezborodov. Virus under the microscope. Novosibirsk State Television and Radio-broadcasting Company, 27 October 2005, URL <http://novosibirsk.rfn.ru/rnews.html?id=9571&cid=7>, accessed 28 October 2005

176 Udmantsev V. Russian Military Microbiology - Ministry of Defence Virology Centre turned 50. Voenno-Promyshlenniy Kuryer, No. 16 (33) 28 April - 11 May 2004, 28 April 2004, URL <http://www.vpk-news.ru/article.asp?pr_sign=archive.2004.33.articles.rostrum_01>, accessed 3 May 2004

The CSDT is clearly taking an active part in outbreaks of severe diseases, and is integrated with the Virology Centre. So far, the contribution of the CSDT is more to the epidemiological protection against naturally occurring diseases but there is no doubt that the CSDT is a part of the Russian system combating bioterrorism.

Volgograd institute and centre

The Volgograd Anti-Plague Institute

The Russian anti-plague system for epidemiological monitoring, prevention and combat of diseases is a continuation of the Soviet system that was developed from the first anti-plague laboratories and stations created in the late Czar period.[177] In Soviet times there were six institutes, 82 stations and field stations plus 200 epidemiological teams, arranged in four tiers and employing up to 14 000 persons.[178]

The Soviet anti-plague system was involved in the work on protection against bioweapons already in the 1950s.[179] During the last phase of the Soviet offensive programme in 1972-1991, one of the anti-plague institutes, possibly in Volgograd, was drawn into research on the genetics of virulence in pathogens for this programme.

In todays Russia, the system consists of five research institutes (in Volgograd, Saratov, Stavropol, Rostov-on-Don and Irkutsk), 11 stations, and 14 units in operation at natural disease foci.[180] The anti-plague system also suffered from the financial difficulties of the 1990s.[181] The anti-plague institutes are research facilities with close cooperation[182], the anti-plague stations and field stations more focused on monitoring. Some institutes also produce vaccines.[183] There are specialised epidemic control teams, SPECTs[184], i.e. mobile civilian teams created by the MoH in 1964 for BW detection in wartime.[185] Recently, it was reported that many facilities are dilapidated and that staffing of the anti-plague system has decreased by 40-50 %.[186] Possibly, facilities that ended up outside Russia were more severely hit, as they

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177 I V Domaradsky and W. Orent. The memoirs of an inconvenient man: Revelations about the biological weapons research in the Soviet Union. Critical Reviews in Microbiology, Vol 27, No. 4 pp. 239-266, 2001.

178 Alevtina Izvekova. Issue Brief: International Assistance for Anti-plague Facilities in the Former Soviet Union to Prevent Proliferation of Biological Weapons. Center for Nonproliferation Studies (CNS), June 2005, URL <http://www.nti.org/e_research/e3_65a.html>, accessed 24 November 2005

179 Domaradsky, I.V., and W. Orent. 2001. The memoirs of an inconvenient man: Revelations about the biological weapons research in the Soviet Union. Critical Reviews in Microbiology 27, 239-266, 2001.

180 Onischenko GG, Sandakhchiev LS, Netesov SV, Martynyuk RA. 2003. Bioterrorism: A national and global threat. Vestnik Rossiyskoy Akademii Nauk 73, 195-204,.

181 Izvekova, A. Issue Brief: International Assistance for Anti-plague Facilities in the Former Soviet Union to Prevent Proliferation of Biological Weapons. Center for Nonproliferation Studies (CNS), June 2005, URL <http://www.nti.org/e_research/e3_65a.html>, accessed 24 November 2005

182 O Reshetko. Life of the NII Saratov "Mikrob" - reality and future. Farmatsevticheskiy Vestnik, No. 33 (No. 149), 1-10 December 1999, URL <http://www.pharmvestnik.ru/issues/0149/documents/0149013.htm>, accessed 9 September 2005

183 Westerdahl, K.S. 2001. Building and Measuring Conficence. The Biological and Toxin weapons convention and Vaccine Production in Russia. FOI-R—0189—SE, 2002.

184 In Russian: СПЭБ; специализированная противоэпидемическая бригада. Domaradskiy's autobiography, Chapter "Fifth Problem", http://www.domaradsky.ru/life.htm#Пятая%20проблема.

185 I V Domaradsky and W. Orent., p.240

186 Izvekova, A. Issue Brief: International Assistance for Anti-plague Facilities in the Former Soviet Union to Prevent Proliferation of Biological Weapons. Center for Nonproliferation Studies (CNS), June 2005, URL <http://www.nti.org/e_research/e3_65a.html>, accessed 24 November 2005

were cut off from funding by Moscow in 1992.[187] The anti-plague system has now become a focus of interest for threat reduction efforts and security up-grades, and funding to this aim will probably increase.[188]

Volgograd Anti-plague Institute traces its origins back to the Imperial Anti-plague Laboratory founded in 1911. Today's institute was established in 1971 in Volgograd.[189] In 2004, the institute, as a part of the anti-plague system, was transferred from the Ministry of Health to the Federal Service for Control in the Sphere of Consumer Rights and Human Wellbeing (Rospotrebnadzor), which in turn is one of the agencies of this Ministry.[190] The institute is funded by the MoH. Onishchenko has asked the VAPI director to earmark funds in the 2006 budget for restoration of the institute's buildings.[191]

It is headed by Vladimir Valerevich Alexeev, a senior scientist from the institute, since 2003.[192]

The Russian information within the BTWC comprises the following activities of the Volgograd API:[193]

- Improvement of methods for detection of the pathogens for glanders and melioidosis,
- Development of prophylactic agents and treatments, and methods of disinfection,
- Microbiological studies of the pathogens for glanders and melioidosis,
- Studies of the efficiency of methods of immunisation, and
- Research on deep mycoses.

The institute also provides education and training, e g in mycosis, for specialists of the local and regional Sanitary-Epidemiological Monitoring Service. In 1996 the aims of the institute were described as follows:[194]

- Anti-epidemic protection of the population,

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187 Gulbarshyn Bozheyeva, Yerlan Kunakbayev, Dastan Yeleukenov. Former Soviet Biological Weapons Facilities in Kazakhstan: Past, Present and Future. Monterey Institute of International Studies, Center for Nonproliferation Studies, Occasional paper No.1, June 1999, URL <http://www.cns.miis.edu/pubs/opapers/op1/.>.

188 David Ruppe. U.S. Helps Secure Former Soviet "Antiplague" Sites. Global Security Newswire, 23 November 2005, URL <http://www.nti.org/d_newswire/issues/print.asp?story_id=BD407922-6931-4271-89F1-B72273258F64>, accessed 24 November 2005

189 Alexey Papyrin. 'Where contact with dangerous infectious diseases is conciously made', Meditsinskaya gazeta, No. 5, p. 5, 17 January 1996.

190 Russian Government Information about facilities and biological activities of the Russian Federation, related to the Biological and Toxin Weapons Convention 1972, Confidence-Building Measures, 13 April 2005.

191 Protocol from a meeting between GG Onishchenko and the heads of the territorial directorates and anti-pest establishments of the Southern Federal Okrug. Federal Service for Consumer Rights and Human Wellbeing, 14 April 2005.<http://www.gsen.ru/doc/prot/20050414.html>, accessed 1 June 2005.

192 Alexeev represented the institute as its director at a scientific conference in Oct. 2003; R2701 . Programme of the conference "Contemporary technology and diagnostics of especially dangerous infectious diseases". Mikrob API, Saratov, 30 September 2003, URL <http://www.microbe.ru/news/index.asp?page_type=1&id_header=8>, accessed 24 November 2004

193 Russian Government Information about facilities and biological activities of the Russian Federation, related to the Biological and Toxin Weapons Convention 1972, Confidence-Building Measures, 13 April 2005.

194 Alexey Papyrin. 'Where contact with dangerous infectious diseases is conciously made', Meditsinskaya gazeta, No. 5, p. 5, 17 January 1996.

- Creation of new materials and methods of laboratory diagnostics of pathogens of especially dangerous infections, e g for fungal infections, dangerous deep mycoses; the institute ensures that sanitary-epidemiological services has the "necessary selection of diagnostic preparations", and
- Furthermore, to define/determine the regulations confirmed by the Sanitary-Epidemiological Monitoring Service Committee of Russia.

Facilities and resources

The institute consists of several research departments, a strain collection, and a laboratory animal breeding facility and a high-safety aerosol laboratory.[195] In 1996, there were six research departments, including 16 laboratories, and the equipment was described as modern. There are seven laboratories with a total area of 1750 m^2 with safety level BL-3, but no BL-4 areas.[196] There is also a patent–information service, library and other information resources, probably including internet.

In 1994, two centres became integrated in the institute, the Federal Centre for Indication and Laboratory Diagnostics of Deep Mycoses and the regional Privolzhk and Ural Rayon Centre for Indication and Laboratory Diagnostics of Pathogens of Especially Dangerous Bacterial Infections.[197]

Since 1999 a third centre is located there, the Federal Interagency Centre (FIAC), which is in focus of this study. The centre was founded to make a significant contribution to the protection and prevention of bioterrorism in the country.

The institute staff appears to be well qualified. In 1996, 10 doctors and 55 candidates of science worked there, and over 20 specialists had then gone through a course in molecular biology given by the RAS.[198] The staff of the aerosol laboratory is included in the specialised anti-epidemiological brigade that performs diagnostic and preventive measures in Russia.[199]

The institute's aerosol facility, the Laboratory of Air-Borne Contaminations, was built in 1994-1996 on the banks of Volga. It is described as a modern laboratory meeting all the necessary requirements. For example, the safety level for staff and environment is said to make it possible to conduct a broad range of experiments with biological material of high pathogenicity. The main scientific aim is to study bacterial aerosols of Pseudomonas (Burkholderia) and other air-borne infections, and to perform work on ecological problems related to effects of industrial aerosols.[200]

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195 Alexey Papyrin. 'Where contact with dangerous infectious diseases is conciously made', Meditsinskaya gazeta, No. 5, p. 5, 17 January 1996.

196 Russian Government Information about facilities and biological activities of the Russian Federation, related to the Biological and Toxin Weapons Convention 1972, Confidence-Building Measures, 13 April 2005.

197 Alexey Papyrin. Where contact with dangerous infectious diseases is conciously made. Meditsinskaya gazeta, No. 5, p.5, 17 January 1996.

198 Alexey Papyrin. 'Where contact with dangerous infectious diseases is conciously made', Meditsinskaya gazeta, No. 5, p. 5, 17 January 1996.

199 Alexey Papyrin. 'Where contact with dangerous infectious diseases is conciously made', Meditsinskaya gazeta, No. 5, p. 5, 17 January 1996.

200 Alexey Papyrin. 'Where contact with dangerous infectious diseases is conciously made', Meditsinskaya gazeta, No. 5, p. 5, 17 January 1996.

The institute's research is reported in numerous publications, reflecting its areas of competence, as described below.

Areas of competences of the Anti-Plague Research Institute

This review comprises over 120 publications in the period 1985-2004 by the Volgograd API (Appendix D). The research at the institute has for decades mainly been focused on the bacterial species of the family Burkholderia (former Pseudomonas)[201] causing glanders (*B. mallei*) and melioidosis (*B. pseudomallei*). Glanders and melioidosis are endemic in some regions of the Russian Federation and the glanders bacterium is also highly ranked on biological warfare list.[202] In addition, pathogenic bacteria such as *Yersinia pestis* (plague) and its less pathogenic relative *Y. pseudotuberculosis*, *Vibrio cholerae* (cholera), *Bacillus anthracis* (anthrax) and the fungi *Coccidioides immitis* (coccidioidomycosis)[203] and *Cryptococcus neoformans* (cryptococcosis)[204] have been studied.

In order to make a brief assessment of the areas of competences of the Volgograd API, a review of the publications from two decades, 1985-2004, has been performed.[205] The publications in scientific journals are presumed to provide a common view of the research and the competence of the institute.

The 30 publications in the first years of the reviewed period (1985-1989) report on the development of various methods, such as electrophoresis and fluorometric tests, for the basic microbiological research. Many publications reflect an interest in using magnetic sorbents in methods for immunological analysis of microorganisms and their antigens. The method was for example used for analysis of antigens of *Y. pestis* and *Burkholderia* as well as the cholera enterotoxin. Magnetic sorbents were used also for the fixation and disinfection of microbial cells. The entrapping of various substances in liposomes was studied, for instance the delivery of antibiotics and antigens for immunisations. Epidemiological studies were made on natural and imported cases of melioidosis and the issue of reservoirs in nature was addressed.

Much emphasis was on the characterisation of pathogenic organisms and their antigens. In addition, experimental infection animal models were developed. Methods for transfer of genetic material between bacterial cells were tested.

In the subsequent period, 1990-1994, the many publications (about 40 % of the reviewed publications) reflect a great interest in pathogenesis. Variants of the pathogenic organisms were characterised and the interaction between the pathogens and their hosts was studied. The production of various antigens related to the pathogenesis was also of interest.

An interest in aerosols was reflected by a paper on the stability of bacterial aerosols in static conditions. Infection by aerosol was used as a standard method in many of the experiments during the entire period of twenty years. Moreover, the effectiveness of treatment of experi-

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201 Many publications use the former name Pseudomonas, but Burkholderia is consistently used in this text.

202 Vorobev, A.A. 2001. Evaluation of probability of use of bioagents as biological weapons. Epidemiol. Infect. Dis. No. 6, 54-56. See Appendix A.

203 Coccidioidomycosis is primary a pulmonary form of disease. The infection can disseminate to all parts of the body, especially the meninges.

204 Cryptococcosis is a disseminated mycosis that manifests itself primarily as meningitis.

205 These publications which authors have affiliation Volgograd API were found in the two literature data bases Biosis and MedLine (PubMed).

mental glanders after infection by aerosol was addressed. The sensitivity of *Burkholderia* to currently used antibiotics and problems of resistance were also reported in this period.

A diagnostic system based on magnetic sorbents and liposomes was designed and immunochemical and radioimmunological methods were further tested. In addition, the use of genetic diagnostics was reported. The studies also addressed the issue of fed-batch cultivation including bacterial growth kinetics.

An apparent reduction in publications was noticed in the years 1995-1999. Similarly to the previous period, the majority of the papers were focused on the interaction between pathogens and host cells and the various antigens that have potential role in pathogenesis. The effectiveness of chemotherapy and affecting factors were other issues of interest. The genetic studies were focused on insertional mutations and plasmid characterisation.

The papers reflect that the scientists tried to improve the immunoglobulin preparations and one result was the design and isolation of monoclonal antibodies.

In the period 2000-2004 the use of genetically based methods for the identification and the problem with multiple antibiotic resistances was reported. Further characterisation of antigens and the response after immunisation with antigens was studied. The possibility of using a genetically modified bacterial (*Francisella*) vaccine strain harbouring a plasmid with *Burkholderia* genes was addressed. Other papers focused on the extrachromosomal hereditary fate at cultivation and plasmid transfer between heterologous species. The influence of heterologous bacilli on the infectious process of the anthrax bacterium was experimentally studied.

In common with the Virology Centre no international publications were found. All the reviewed papers were written in Russian and published in Russian journals. The affiliations of the authors of the publications reflect that the scientists of the Volgograd API have an extensive net of contacts by collaboration with various research institutes in the Russian Federation:

- The Anti-Plague Institutes (Research Institute of Plague Control) in Saratov, Rostov, Stavropol and Irkutsk
- The Ivanovsky Research Institute of Virology in Moscow
- The Sechenov Moscow Medical Academy in Moscow
- The Gamaleya Research Institute of Epidemiology and Microbiology in Moscow
- The N.D. Zelinsky Institue of Organic Chemistry in Moscow
- The I.T. Mechnikov Research Institute of Vaccines and Sera in Moscow
- The Russian State Technology University in Moscow
- The Volgograd State Technical University in Volgograd
- The Volgograd Medical Academy in Volgograd
- The St. Petersburg State University in St. Petersburg
- The Pacific Ocean Research Institute of Fish Industry and Oceanography in Vladivostok

Furthermore, cooperation has been performed with the Russian State Committee for Sanitary and Epidemiology Surveillance in Moscow.

In accordance with the affiliations of co-authors of scientists of Volgograd API, the institute also has collaboration also with foreign establishments:

- The Anti-Plague Research Institute in Sofia, Bulgaria
- The Kyiv Scientific-Research Institute of Epidemiology and Infectious Diseases in Kyiv, Ukraine

In the section below the published research is presented as areas of competences.

Epidemiology

Epidemiological studies have been performed on the causative agents of melioidosis, glanders, pseudotuberculosis, cholera and plague. It was found that the *Burkholderia* and *Y. pseudotuberculosis* have all the necessary potentials for active soil existence. In contrast, *Y. pestis* has no such potential.[206]

The phenomenon of carrier-state of infectious agents was one issue of interest and methods were developed to study the persistence of bacteria in hosts of natural foci.[207, 208] It was shown that L-forms of for instance *Y. pestis* could persist in host animals and in carriers such as mites for long time (years).[209] Radioimmunological analysis was used to study the persistence of *Y. pestis* in rodents and ectoparasites in natural foci.[210]

The epidemiological characteristics, life strategy and self-regulation mechanisms of populations of *Burkholderia* were studied and a method to determine reservoirs was developed.[211,212,213,214] It was suggested that L-transformation may explain chronic *Pseudomonas* carrier state.[215]

The epidemiology of cholera in some regions of the former Soviet Union was determined.[216]

The absence of coccidioidosis in Russia was explained by the existence of other organisms which produced inhibitory substances in the normal habitat of the fungus. Moreover, these substances were shown to stimulate the conversion of *Coccidioides* and other fungus from the mycelia form into the yeast form, which results in the death of the fungi.[217, 218, 219]

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206 Larinov, G.M., and N.I. Pogasii, 1995

207 Manolov, A.D., 1985

208 Manolov, A.D., et al., 1991

209 Zykin, L.F., G.S. Dunaev, S.R. Sayamov, and P.S. Sokolov. 1989

210 Manolov, A.D., et al., 1991

211 Larinov, G.M., and V.D. Belkiakov, 1990

212 Larinov, G.M., 1987; 1988

213 Federov, A.I., 1986

214 Federov, A.I., G.M. Larionov, and Iu.S. Golov, 1986

215 Zamaraev, V.S., et al., 1987

216 Lobanov, A.N., et al., 1995

217 Shelokhovich, A.I., V.S. Lesovoi, and P.M. Lashchenov, 1991

218 Lesovoi, V.S., A.I. Shelokhovich and A.V. Lipnitskii, 1993

219 Shelokhovich, A.I. V.S. Leovoi, and A.V. Lipnitskii, 1991

Volgograd API has a library of bacterial, yeast and fungus strains. The institute's strain collection is stated to consist of 69 species and 910 strains of bacteria, 13 species and 73 strains of fungi, and 6 species and 2 strains of yeast.[220] The collection of Burkholderia/Pseudomonas strains is said to be one of the best in Europe with both endemic strains isolated in Russia and hundreds of strains from South-East Asia and Europe. At least one plague strain (Yersinia) is maintained. The collection of deep mycosis pathogens has been described as unique.[221]

Growth and stability of bacteria in various systems

The optimal conditions of batch cultivation of bacilli were evaluated in order to increase the efficiency of culturing and to maintain the morphology of the bacterial cells.[222] The reproducibility was tested on *Bacillus* cells.

The growth kinetics of *Pseudomonas putida* and its determining factors were also evaluated.[223]

Biomass accumulation in vitro and proteolytic enzyme synthesis in *B. pseudomallei* were determined. Studies were performed on the dynamics of main antigens of the pathogenic *Burkholderia* species during cultivation.[224]

A medium for transport of samples containing pathogenic *Pseudomonas*/*Burkholderia* was developed.[225] Material infected with *B. mallei* or *B. melioidosis* was shown to be preserved for 5-7 days.

Animal model systems

Animals were used in experimental infections in order to study the pathogenesis and the effect of immunisations, for instance studies on capsule formation in melioidosis and the interaction of *B. pseudomallei* with immune cells in vivo.[226, 227, 228] Several publications present the results of antibiotic treatment of animals which had been exposed to aerosolised bacteria.[229, 230, 231]

An experimental study was performed on the influence of heterologous bacilli in the infectious process of *B. anthracis*.[232]

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220 Genetic and Biological Collections of the Russian Federation, information on the internet, URL http://www.sevin.ru/collections/microcoll/coll_list/coll3.html, accessed 17 January 2005

221 Alexey Papyrin. 'Where contact with dangerous infectious diseases is conciously made', Meditsinskaya gazeta, No. 5, p. 5, 17 January 1996.

222 Stepin, A.A. et al., 1994.

223 Samygin, V.M. et al., 1994.

224 Samygin, V.M. et al., 2001.

225 Zhoga, L.K., V.I. Iliukhin, and V.M. Samygin, 1995.

226 Melnikov, B.I., et al., 1990.

227 Popov, S.P. et al., 1990.

228 Popov, S.P., V.Ia. Kurilov and M.P. Lagutin, 1992.

229 Iliukhin, V.I., et al., 1994.

230 Batmanov, V.P., 1991; 1993; 1994.

231 Batmanov, V.P., et al., 1994.

232 Bulantsev, A.L., and A.V. Lipnitsky, 2000.

In evaluating the possibility of peroral immunisation to *Coccidioidomyces*, fungal culture was infected directly into the stomach of albino mice.[233] It was found that immunisation with cells of an avirulent fungal strain protected almost 90 % of the immunised animals after challenge with a virulent *Coccidioides* strain.

The animals used in the various model systems were rodents.

Immunology and vaccine development

Burkholderia thailandensis, a *B. pseudomallei*-like low-virulent bacterium, was isolated from environmental sources in regions with endemic glanders. These strains were characterised and their biological properties, identification and taxonomy were reported.[234] Immunisation experiments in animals indicated that these strains were potential melioidosis vaccine strains.

In addition to low-virulent or attenuated *Burkholderia* strains, recombinant *Francisella tularensis* carrying plasmid-located *Burkholderia* fragments were tested in immunisation experiments.[235, 236] Immunised animals with different sensitivity to the pathogen were challenged by aerosol. It was concluded that the genetically engineered *F. tularensis* vaccine was a good candidate for a future vaccine to *B. mallei*.

Various surface antigens and antigen complexes of *B. pseudomallei* were examined for immune stimulating activity in animal hosts.[237, 238, 239] A *Burkholderia* glycoprotein was found to be common in the cell fractions having protective properties.

Magnetic sorbents were prepared and used in studies of bacterial antigens and the antigenic properties of fractions of *Burkholderia* were, for instance, examined by monitoring the antibody response. [240, 241]

The prospect for using anti-idiotypic antibodies for vaccination was discussed.[242] There is, however, no publication on the successful development.

Vaccine studies were performed also on *B. anthracis* infections by focussing on the antibody response from common antigens after immunisation.[243] The possibility to increase survival of animals by adding vaccine or avirulent strains together with virulent *Bacillus* strains was experimentally shown.[244]

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233 Prokof'eva, E.I., et al., 1985.

234 Iliukhin, V.I., et al., 2002.

235 Iliukhin, V.I., et al., 1999.

236 Iliukhin, V.I. et al., 2004.

237 Piven', N.N., 1987.

238 Barkov, A.M., V.Iu. Perov, and V.G. Pushkar', 1989.

239 Avrorova, I.V., et al., 2004

240 Pushkar', V.G., et al., 1985.

241 Barkov, A.M., V.Iu. Perov, and V.G. Pushkar', 1989.

242 Likholetov, S. M., and V.Yu. Sorokin, 1986.

243 Barkov, A.M., et al., 2000.

244 Bulantsev, A.L., and A.V. Lipnisky, 2000.

Various surface antigens of *Y. pestis* were entrapped in liposomes and these complexes were used for immunisation of animals.[245, 246] Immunisation with liposomal capsule antigen as well as major somatic antigen of the plague agent gave rise to an increased protective effect.

Studies of genetics and pathogenesis

The issue of elucidating the infectious process caused by *Burkholderia*/*Pseudomonas* was addressed from various points of view. Basic studies of the interaction of *B. mallei* and *B. pseudomallei* with the host and its immune system were reported.[247, 248, 249] Spontaneous genetic transformation has been found in *B. pseudomallei* and when infecting a host *Burkholderia* rapidly adapts to the host species by the transforming its antigenic structure.[250,251] Various genetic and biologic aspects of *B. pseudomallei* were discussed in a review.[252]

The phage-producing activity and sensitivity of various *B. mallei* strains from a strain collection was found to differ and some strains were demonstrated to lack phages.[253, 254] Bacteriophages were isolated and morphologically classified.[255] The phages are possible diagnostic tools for *B. mallei*. No phages were demonstrated in *B. pseudomallei*.

Various attempts to develop a genetic system in *Burkholderia* have been reported.[256, 257, 258, 259] Initial experiments included the transfer of heterologous plasmids into *B. mallei* and *B. pseudomallei* and the demonstration of expression of new determinants, mainly resistance markers.[260] In parallel to the attempts to transfer genetic material into/from *Burkholderia*, various pathogenicity factors were identified.[261]

Four cryptic plasmids were isolated from *B. mallei* and these plasmids were characterised by various methods.[262, 263] The isolation and characterisation of plasmids lead to the development of a genetic system in the melioidosis bacteria. By using one of the cryptic plasmids from *B. mallei* it was possible to transfer genetic material to heterologous species.[264] The effect of

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245 Zakrevskii, V.I., N.G. Plekhanova, and V.I. Smirnova, 1989.

246 Zakrevskii, V.I. and N.G. Plekhanova, 1990.

247 Iliukhin, V.I., 1985; 1986.

248 Popov, S.F., V.Ia. Kurilova, and M.P. Lagutin. 1992.

249 Popov, S.F., V.Ia. Kurilov, and B.I. Melnikov, 1991.

250 Bulantsev, A.M., and N.A. Lozovaia, 1985.

251 Larinov, G.M., 1988.

252 Zakharova, I.B., 2000.

253 Denisov, I.I., and V.I. Kapliev, 1991.

254 Grishkina, T.A., and L.K. Merinova, 1993.

255 Denisov, I.I., and V.I. Kapliev, 1995.

256 Ageeva, N.P., and L.K. Merinova, 1986.

257 Bulantsev, A.L., and N.A. Lozovaia, 1985.

258 Ageeva, N.P., L.K. Merinova, and M.K. Peters, 1989.

259 Seimova, I.K., L.K. Merinova, and M.K. Peters, 1988.

260 Anishchenko, M.A., and L.K. Merinova, 1992.

261 Anishchenko, M.A., 1991.

262 Zamaraev, V.S., et al., 1998.

263 Zakharova, I.B., D.V. Viktorov, and V.S. Zamaraev, 2000.

264 Merinova, L.K., et al., 2000.

cultivation temperature on the extrachromosomal hereditary fate was studied.[265] In order to create genetic changes in the *Burkholderia* genome, various transposons were used.[266]

The presence of a protective slime layer was investigated and in 1990 the presence of a capsule of *B. mallei* was reported.[267, 268, 269, 270, 271] The acid exopolysaccharide was isolated and it was found to inhibit macrophages.[272, 273] Moreover, the exopolysaccharide was shown to form a protective surface structure which enhance the viability of bacteria – including heterologous species - in aerosol.[274] Studies of the fate of encapsulated *B. mallei* in the body of animals showed that it parasitized mainly in phagocytes in the liver, spleen and the lungs.[275] In common with *B. mallei*, *B. pseudomallei* has a capsule.[276] A comparison of the capsular material of the two species showed that they were similar in their composition, indicating the close relation of the two strains.[277, 278] Moreover, chromatographic fractions of the surface components of both species were scanned for immunologic effect and several fractions were shown to have immunomodulating properties. One of the pathogenicity factors of *B. pseudomallei* which has been characterised has an anti-phagocytic action.[279] This component, the antigen 8, was considered to be one of the key pathogenicity factors of *B. pseudomallei*.[280] The production of the antigen in *B. mallei* and *B. pseudomallei*, respectively, was studied and the location of the antigen was determined by the use of monoclonal antibodies and electron microscopic analysis.[281, 282] Monoclonal antibodies were used for studies of enzyme-antienzyme interactions.[283]

Several additional components with presumed importance for the virulence have been described. For instance, the chemical nature of a thermostable hemolysin of *B. pseudomallei* was investigated.[284] The various components of pathogenicity such as capsule-like structures

[265] Antonov, V.A., et al., 2003.

[266] Merinova, L.K., E.V. Timofeeva, and I.K. Simova, 1997.

[267] Denisov, I.I., 1985

[268] Popov, S.F., V.Ia. Kurilov, and B.I. Mel'nikov, 1991

[269] Popov, S.F., V.Ia. Kurilov, and A.T. Iakovlev, 1995

[270] Mel'nikov, B.I., et al., 1990

[271] Kapliev, V.I., I.I. Denisov, and V.Ia. Kurilov, 1990

[272] Popov, S.F. et al., 1990

[273] Bozhko, V.G. et al., 1992

[274] Denisov, I.I., et al., 1992

[275] Popov, S.F. et al., 2000

[276] Popov, S.F., V.Ia. Kurilov, and A.T. Iakovlev, 1995

[277] Popov, S.F., et al., 2002

[278] Piven', N.N., et al., 2001

[279] Piven', N.N., et al., 1996

[280] Piven', N.N., et al., 1991

[281] Samygin, V.M. et al., 2001

[282] Kapliev, V.I., N.N. Piven', and N.P. Khrapova, 1992

[283] Tikhonov, N.G., et al., 1999

[284] Denisov, I.I., et al., 1996

including antigen 8, exoproteases, hemolysins, endotoxin, and lecithinase have been reviewed.[285] In addition, a glycoprotein of *B. pseudomallei* was reported.[286]

Experimental studies were performed also on the enzyme system of *B. mallei* and, for instance, the properties of an extracellular alkaline phosphatase were described.[287, 288]

The dependence of plasmid content on the fate of *Bacillus* spores in laboratory animals was verified by inoculation into guinea pigs of spores of *B. anthracis* strains which had different plasmid composition. Germination of the spores occurred as early as in two hours for all the strains studied, but the further fate depended on the plasmid composition of each strain.[289] It was made clear that one of the plasmids mediated protection to phagocytosis, while the other plasmid harboured genes for toxin production.

There were only a few papers on the plague agent *Yersinia pestis* available for review. A virulence factor of *Y. pestis*, which was studied, was demonstrated to be a capsular antigen.[290] Moreover, the fatty acid composition of *Y. pestis* was described.[291]

An experimental animal model was developed for *Coccidioides immitis* and the pathogenicity of the fungus was studied from various aspects, for instance the tropism in the lung.[292, 293] The specificity of antigens was elucidated and the enzymatic nature of some *C. immitis* antigens was described.[294, 295, 296] A transplantation test was used to demonstrate the presence of heterologous antigen in highly virulent strains of the fungal. These antigens cross-reacted with antigens of human erythrocytes and with skin of white mice.[297] Fungal variants with different virulence were isolated and spontaneous morphological variants of *C. immitis* were described.[298, 299]

Treatment

A number of drugs such as gentamicin, doxycycline, sulphanilamide, and quinolones were tested on animals experimentally infected by *B. mallei* in aerosol.[300, 301, 302] The studies com-

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285 Piven', N.N., and V.I. Iliukhin, 2000

286 Khrapova, N.P., N.G. Tikhonov, and E.V. Prokhvatilova, 1998

287 Narbutovich, N.I., n.G. Tikhonov and I.M. Klimatova, 1999

288 Narbutovich, N.I., Iu.A. Goloseev, and T.G. Varykhanova, 1991

289 Popov, S.F., et al., 1996

290 Manolov, A.D., et al., 1987

291 Samygin, V.M, et al., 1993; 1994

292 Prokof'eva, E.I. et al., 1985

293 Lesovoi, V.S. and E.I. Prokof'eva, 1990

294 Lesevoi, V.S., A.I. Shelokhovich, and N.Y. Vysochinskaya, 1989

295 Rogozhkina, N.M, and A.V. Lipnitskii, 1986

296 Rogozhkina, N.M, et al., 1989

297 Orudzheva, N.V. et al., 1992

298 Lipnitskii, A.V. et al., 1993

299 Shelokhovich, A.I., et al., 1988

300 Iliukhin, V.I. et al., 1994

301 Lozovaia, N.A., 1989

302 Batmanov, V.P., 1991; 1993; 1994

prise transport of antibiotics across membranes and the development of methods for the control of effectiveness of treatment and antibiotic resistance. The sensitivity of pathogenic *Burkholderia* as a function of medium temperature and pH was monitored and the recovery rate was determined.[303, 304, 305, 306, 307, 308]

The use of liposomes in treatment, prophylaxis and diagnostics was paid attention as early as 1985.[309] The incorporation of antibiotics in liposomes has been tested and a method for sterilisation of these vesicles was published.[310]

Diagnosis

Various methods for rapid diagnosis of glanders and melioidosis were developed and tested.[311] Chemiluminescent and immunofluorescent immunoassays which permit reliable diagnosis within 3-12 hours were reported.[312, 313, 314, 315, 316, 317] The adsorptive capacity of magnetic immunosorbents was elucidated.[318] The two forms of disease could be differentiated by immunoassays.[319] The potential of monoclonal antibodies in detection of *Burkholderia* was evaluated by studying the conditions for the interaction of the antigens and monoclonal antibodies.[320, 321]

Genetic identification methods have also been developed; Based on *B. pseudomallei* plasmid DNA probes were designed.[322, 323] These were useful for differing between pathogenic *Burkholderia* and related non-pathogenic bacteria which have similar phenotypic and antigenic characteristics. In addition, PCR methods have been used for the identification of *B. mallei* and *B. pseudomallei*.[324, 325] *B. mallei* could be identified in environmental objects as well as in clinical material.

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303 Viktorov, D.V., and N.N. Piven', 2001

304 Batmanov, V.P., V.I. Iliukhin, and Iu. V. Antonov, 1995

305 Antonov, Iu.V. et al., 1991a,b

306 Ferster, L.N., et al., 1986

307 Iliukhin, V.I., and V.P. Batmanov, 1997

308 Batmanov, V.P. et al., 1996

309 Zakrevskii, V.I., 1985

310 Rotov, K.A., V.P. Vasil'ev, and Yu.V. Antonov, 1989

311 Samygin, V.M., T.A. Griskhina, and O.M. Ochkurova, 2004

312 Yakovlev, A.T., L.F. Zykin, and I.V. Zimenkov, 1989

313 Alekseev, V.V., et al. 1994

314 Bykova, O.I., and V.V. Alekseev. 1986

315 Podzolkova, G.G. et al., 1988

316 Dunaev, G.S., et al., 1992

317 Piven', N.N., et al., 1994

318 Podzolkova, G.G., et al., 1988; 1989

319 Dunaev, G.S. et al., 1995

320 Iakovleva, I.V., et al., 1995

321 Khrapova, N.P. et al., 1995

322 Antonov, V.A., et al., 2000

323 Antonovm V.A., V.S. Zamaraev, and V.I. Iliukhin, 1998

324 Antonov, V.A., et al., 2004

325 Tkachenko, G.A:, et al., 2003

It was demonstrated that by using a solid-phase enzyme immunoassay circulating immune complexes and antibodies could be detected in individuals infected by *B. mallei* and *B. pseudomallei.*[326] This test was concluded to be a useful tool to predict the outcome of these infectious diseases.

Species-specific DNA probe for the identification of *B. anthracis* strains has been constructed.[327, 328] Toxin-producing anthrax strains were possible to identify and to differentiate from other species of *Bacillus* as well as from bacteria of other taxonomic groups.

Y. pestis was used as model organism in evaluating the possibility to use magnetic sorbents for the construction of a diagnostic assay system based on antigen-antibody interaction.[329, 330]

The problems of laboratory diagnosis of deep mycoses have been discussed in a review. [331] Solid-phase immunoenzyme methods were shown to be useful for analysis in medical mycology, for instance for *Coccidioides immitis* antigens.[332, 333] Hybridoma technology was used to produce monoclonal antigens for diagnostically significant antigens of *Cryptococcus neoformans*, the infective agent of cryptococcosis, and these antibodies were used in various assays such as immunofluorescence, cytochemical and solid-phase enzyme immunoassays.[334]

Means to detect the cholera enterotoxin were of interest in the few publications on *Vibrio cholerae* which were found. The method of choice was a quantitative immunofluorescence assay based on the selective sorption of cholera enterotoxin by gangliosides in polyacrylamide granules.[335, 336, 337]

Moreover, methodological aspects of the study of bacterial chemotaxis were presented in one paper.[338]

Aerosol techniques and stability of biological aerosols

Infection via aerosol was commonly used in animal model systems for tests of antibiotics and in vaccine studies (see previous sections). The problem of retaining the stability of bacterial aerosols was addressed in one of the papers.[339] The exopolysaccharides of *Burkholderia* species, which has been shown to form a protective layer around bacteria, was demonstrated to enhance the viability of bacteria in aerosol.[340] The protection was apparent both in the process

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326 Dunaev, G.S., et al. 1992, 1994

327 Timoshin, V.B., et al., 1994

328 Timoshin, V.B., V.S. Zamaraev, and A.V Lipnitskii, 1995

329 Klimova, I.M., V.I. Efremenko, and V.G. Pushkar', 1989

330 Vladimtseva, I.V., et al., 1990

331 Lipnitskii, A.V., et al., 1995

332 Khrapova, N.P., N.M. Rogozhkina, and S.F. Zharkova, 1988

333 Khrapova, N.P., 1989

334 Khrapova, N.P. et al., 1999

335 Vladimtseva, I.V., et al., 1986; 1988

336 Dolmatova, L.A. et al.,1985

337 Trofimov, E.N., et al., 1987

338 Likholetova, S.M, A.N. Akhmedov and V.A. Zharkova, 1986

339 Denisov, I.I. et al., 1992

340 Denisov, I.I., et al., 1992

of generation of aerosol and during its suspension in the air under static conditions with different values of relative humidity.

The Federal Interagency Center in Volgograd

The Federal Interagency Centre for training specialists, and testing means and methods of indication of pathogens causing extremely dangerous infections (FIAC) was established on 30 July 1999 by a decree of the MoH, as a consequence of the decision of the Federal Anti-terrorist Committee (FAK) on 16 February 1999 (Appendix E).[341] According to General Evstigneev, an expert on biological defence, the establishment of the FIAC is one of five major measures taken by the Russian government to counteract bioterrorism (cf.list on p.8).[342]

It is located at the Volgograd API and N.G. Tikhonov, then head of the API, was appointed to head also the FIAC. Presumably, the directorship has passed on to the current director of the anti-plague instititute, V.V. Alekseev. A Scientific-Technical Council, with representatives from the Volgograd API and interested ministries and departments, supports the Head of the Centre in questions on the activities of the Centre. The ultimate responsibility for the Centre lies with the First Deputy Minister of Health, Onishchenko, and the MoH finances the Centre.[343]

The primary aim of the Centre is to counteract bioterrorism and protect the population against such acts. Briefly, the Centre is the ”coordinating, advisory-methodical, educational, diagnostic and expert body that also carries out functions of the main establishment on questions of indication and express-diagnostics of potential agents of bioterrorism.” In its activities, it is to interact with the Federal Sanitary-Epidemiological Monitoring Service centres and the Anti-Plague establishments, and also the interested establishments of other ministries and departments.

More specifically the aims of the Centre are:

- Training of experts in indication and express-diagnostics of pathogens of especially dangerous infections (EDI), including improvement of professional skill of doctors and laboratory technicians; and development and improvement of course curricula;
- to provide a uniform base for interdepartmental evaluation and tests of new indication and express-diagnostics methods; updating the indication scheme for pathogens of EDI in view of the latest data;
- to perform and coordinate research on the development and introduction into practice of modern and automated indication methods for pathogens of EDI; and analysis of current research and developing the research directions for Russia in this field;
- To document the activities of the Centre and annually report these to Working Group No. 3 of FAK (see below);
- To provide organizational and methodological help to the public health service;

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341 Ministry of Health. 'Ministry of Health of the Russian Federation, Order No. 300 "On Establishing a Federal Interagency Center", dated July 30, 1999', Ministry of Health of the Russian Federation, 990730; Appendix E.

342 Yevstigneyev, V.I. 'Biological Weapons and Problems of Ensuring Biological Security', lecture at the Moscow Institute of Physics and Technology, 030325.

343 Cf. Appendix E.

- To hold seminars, meetings, scientific conferences, as well as publish on questions of counteraction to bioterrorism;
- To develop platforms of interaction with the establishments of the Ministry of Health, the Ministry of Internal Affairs, the Ministry of Defence, the Ministry of Agriculture and Food Production, FSB and other interested ministries and departments, in assuring measures on the security of facilities that are carrying out work with potentially dangerous bioagents.

Working Group No. 3 of FAK is the interdepartmental working group ”on questions of protection of the population, agricultural animals and plants from possible application by terrorists, terrorist groups or the terrorist organizations of biological, chemical and other agents of a mass lesion, and also to questions of struggle against illegal circulation of potentially dangerous agents and materials”.[344] This group is a permanent working group established on 19 March 1999 in the Ministry of Health, and Onishchenko was charged with the control of its performance.[345]

Searches in open sources have yielded relatively little information on the FIAC activities and priorities, funding and staffing, etc. The educational role of the FIAC is clear from the start as underlined by MoH Instructions on countering terrorism in September 1999, where it is said that education and improvement of professional skills, on a regular basis, will be directed at e.g. doctors-bacteriologists and laboratory assistants of the centres of State Sanitary-Epidemiological Surveillance and antiplague establishments. There are examples of explicitly directing staff for training courses to the FIAC.[346]

The Volgograd API jointly with the MoD Virology Centre developed the programme ”Prophylaxes against especially dangerous and natural-focal infections and sanitary preservation of the territory of the Southern Fedral Okrug of the Russian Federation against introduction and spread of infectious diseases (2002-2005)”.[347] This is clearly a part of the Russian counter-measures against bioterrorism and would be in line with the other tasks of the two new centres rather than their mother institutes.

A description and analysis of the anthrax letters incident in the US was published by Onishchenko and four scientists in 2003. The authors’ affiliations are given as the Ministry of Health and the Volgograd API. The paper discusses how epidemiology can define an outbreak as a bioterrorist attack and trace it to its source. This paper is well in line with FIACs aim to

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344 Joint decree of the Ministries of Health and Internal Affairs and the Federal Security Service, 'No. 03-23/2-11 Regulations About Interaction of the Ministry of Health of Russia, the Ministry of Internal Affairs of Russia and the Federal Security Service of Russia for the Implementation of Control of the Sanitary-Hygienic and Antiepidemic State of Densely Populated Places and actions in the Extraordinary Situations Caused by Acts of Terrorism', www.recipe.ru, January 2000

345 Ministry of Health. 'Order of 19 March 1999, No. 92, about a working group of the Federal Antiterrorist Committee', Ministry of Health, 19 March 1999

346 About measures on counteraction to biological terrorism in Tomsk area. TU Rospotrebnadzora po Tomskoy oblast, 2005, URL <http://snadzor.tsu.ru/Postanovlen/27_4_terror.htm>, accessed 25 November 2005

347 There are 3000 soil foci of anthrax in the Southern Federal District. All Russia, undated, URL <http://www.allrussia.ru/pressreview/default.asp?id=134892&rub_id=16>, accessed 1 June 2005

monitor current research in countering bioterrorism, and could be a product from the FIAC although the affiliation given is the Volgograd API.[348]

In January 2005, 30 unique specialists, including epidemiologists, microbiologists and parasitologists, from the FIAC were preparing to go to South-East Asia as part of the Russian contribution in the aftermath of the Tsunami. The majority of them were very experienced, having visited almost every disease focus including those in Armenia and Chechnya.[349] This special brigade from the Volgograd API was reported to bring diagnostics for ”every possible disease from plague to Dengue fever”.

In 2005 the Centre, together with the Volgograd API and other organisations, organised the Sixth Inter-State Scientific-Practical Conference ”Sanitary Protection of the Territories of the CIS States: Problems of Biosecurity and Counteracting Bioterrorism in Contemporary Conditions”, which included a meeting on biosecurity and countering bioterrorism.[350]

The role of FIAC is confirmed in a meeting with Onishchenko in September 2005. Together with the Centre for Molecular Diagnostics of Infectious Diseases and the Centre for Genetic Diagnostics of Especially Dangerous Infectious Diseases, the Centre has a coordination, normative-methodological and educational-consultational function in the system of the Federal Service for Control in the Sphere of Consumer Rights and Human Wellbeing (Rospotrebnadzor).[351]

The above can be seen as examples of FIAC executing some of its decreed tasks: Training of experts, providing methodological help to the public health service, organising conferences and publishing on counteractions to bioterrorism. No publications were identified to be the result of development and evaluation of modern and automated detection methods at FIAC. Three papers on this topic were published in 2000-2004 by authors affiliated with the Volgograd API. Yet again, other FIAC activities are less likely to become public through the media, such as improvement of course curricula, the annual report of the Centre to Working Group No. 3 of FAK, and developing interactions with other organisations.

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348 Onishchenko G.G., Fedorov Yu.M., Tikhonov N.G., Lipitskiy A.V. and Alexeev V.V. Counteractions against bioterrorism as a new problem for epidemiology. Epidemiologiya i infektsionnye bolezni, No. 2, pp. 3-6, 2003

349 ”Epidemiological special brigade of the Volgograd API sets off for south-east Asia”, 14 January 2005, URL <http://www.volgograd-trv.ru/20050114_fact.asp>

350 Irina Ilicheva. In Volgograd the 6th Interstate Scientific-Practical Conference ”Sanitary maintenance of the territories of the CIS Member States: Problems of biosecurity and bioterrorism counter-measures in the current situation” is held. RIA Novosti, 13 September 2005.

351 Decision No. 21 About perfection of the state sanitary-and-epidemiologic supervision on counteraction to threat of bioterrorism. Federal Service for Control in the Sphere of Consumer Rights and Human Wellbeing, 5 September 2005.

Discussion

Russian concern with terrorism in the 1990s has led to counter-measures to bioterrorism, among them the establishment of two lead centres, the CSDT and the FIAC. They have been in place for over five years now, a time that allows their resources and activities to be described. Based on this information an attempt will be made here to evaluate their level of competence and achievements, also in comparison to the decreed tasks. The competence descriptions include their mother institutes since the decrees creating the two centres indicate that they are not separate entities. Reviewing the available information about the two new centres enhances this impression. The two centres are independent from each other. They were established by separate orders and are funded separately. The aims and areas of activities are different and could be viewed as complementary. The Ministry of Defence is only indirectly involved, if at all, in the activities of the FIAC. There are very few signs of cooperation – only one example was found in open sources.[352]

There are some notable features of the CSDT/Virology Centre and FIAC/Volgograd Anti-Plague Institute, respectively. The CSDT has an unusual not to say unique position in the official structures of Russia as it is subordinated both to the MoD and the Ministry of Health and Social Development (formerly MoH). The decree (Appendix C) clearly places the RCB Defence Force in the structure between the MoD and the CSDT, indicating that the Force is in charge of the Scientific Research Institute (SRI) of Microbiology and its Virology Centre. This is in accordance with information that the Force's Directorate of Biological Protection is responsible for coordinating the work of the institute.[353] The highest tier responsible for BCW issues in the MoD is defined as the First Deputy Minister of Defence and the RCB Defence Force is part of those Forces directly under the MoD. The MoH is represented by the First Deputy Minister of Health who is also the Sanitary Surgeon General. This post is presently held by Gennadiy Onishchenko, head of the Federal Service for Control in the Sphere of Consumer Rights and Human Wellbeing (Rospotrebnadzor) and responsible for the epidemiological protection of Russia. The present place of the CSDT in the organisational structures is not entirely clear. However, the most logical assumption is that the CSDT now is subordinate to the Rospotrebnadzor.

The Virology Centre is a military facility and has often been described as a "closed facility", both by analysts in the West and Russian media. This is true in the sense that no foreigners are allowed to visit the centre, nor does the centre staff have any collaborations with foreign organisations. Access to the facility is apparently restricted, but the centre has a wide net of contacts in the Russian Federation with co-authors on its scientific papers from more than ten facilities. Moreover, the Virology Centre has continuously produced open papers; the present review has identified a low-frequency publication rate, on average five papers per year from 1990. This is equivalent with a certain degree of transparency, although not all results are openly published, and it has been used in this paper for reviewing the competence areas of the

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352 The Volgograd API has joined with the MoD Virology Centre to fight against bioterrorism (undated information, but this specific cooperation occurred not later than 2002). Together they developed the programme "Prophylaxes against especially dangerous and natural-focal infections and sanitary preservation of the territory of the Southern Fedral Okrug of the Russian Federation against introduction and spread of infectious diseases (2002-2005)".

353 Nikolay Poroskov. We were not going to use biological weapons. Vremya Online, URL <http://www.vremya.ru/2003/74/13/35391.html>, 24 April 2003.

Virology Centre. There are certainly additional research results that are classified as this institute is subordinate to MoD and works on means of protection against biological weapons.

The Volgograd Anti-Plague Institute is considered to be an open facility – subordinate to MoH - and it has a comparable number of collaborating institutes in Russia as the Virology Centre. In addition, API has been cooperating with institutes in Bulgaria and Ukraine. In common with the Virology Centre, the Volgograd API has more than 100 publications from 1985, which have been reviewed in this study. Apart from this, there is limited information on the activities of the Volgograd API and the FIAC. It is not known if any classified research is performed at the institute. The initial five years of FIAC is characterised by an almost total silence of its activities.

The information available of the Virology Institute reflects an institute with a fairly good economic situation (compared to many of the Russian research facilities with strained economy). No information was available on the funding of the FIAC, but the few signs of activity of the FIAC could indicate that it is underfunded.

The introduction of the two centres with their prioritised tasks is expected to have stimulated the publications on counter-measures to bioterrorism, i.e. means and methods on new vaccines, identification and treatments. The overall number of publications would also be expected to increase. This is the trend observed in other countries which has directed the efforts on counter measures to bioterrorism. In for instance the US there is a pronounced steam of scientific papers with reports on the clinical test of new vaccines, improved identification methods and also general studies on pathogenic organisms on the priority lists in order to gain a better basic know-how of these virus and bacteria. On the contrary, the review of publications of the two Russian centre/institute reveals that there is a modest number of publications in the new millennium (2000-2004), with a 50 % reduction of the publications from the institute in Sergiev Posad/CSDT compared to the previously two 5-years blocks. API in Volgograd has en even more pronounced reduction in publication frequency, with a rapid decline after 1995. The outcome of the period 1995-1999 is about 50 % of that of 1990-1994, and in the new millennium the publications from API/FIAC amount to only 40 %. Both institutes have somewhat restricted the distribution of their publications by writing in Russian and publicating in domestic journals.

The sudden increase in publication frequency in the 1990s is assumed to reflect a sense of freedom and openness under the Gorbachev era and after the break-down of the Soviet Union. The Russian scientist strived to take part of the international scientific network and to reach this goal they may have made an inventory of their research results and wrote an increased number of scientific papers.

The focus of research at the Virology Centre is remarkable steady in the 15-year interval from 1990 to 2004. In the initial as well as final years of the interval, about one third of the publications have focus on vaccines and approximately 20 % on treatment and identification, respectively. Reported studies on general pathogenesis are reduced from about 20 % of total publications in the first period to approximately 5 % in the last years.

It is concluded from the survey of publications that the Virology Centre/CSDT has an impressive knowledge in some of the most dangerous viruses known. It also has a representative set of methods and equipment for studying such viruses. The centre has a broad range of pathogens under investigation, but only the Marburg virus and the poxvirus Variola are included in the list's group I of bioterrorism agents (Appendix A). On the contrary, neither

Ebola nor Lassa virus which are common objects of the centre's research are found in the priority list. Here, it should be noted that these deductions are made from the openly published research.

At the Volgograd API the publication pattern is somewhat different than at the Virology Centre/CSDT. According to the publications there is much less work done on the development of means of treatment. Identification and detection seem to be important issues at the institute, being the topic of 20 % of the reviewed papers. Papers on vaccine development appear in the later part of the interval and research on pathogenesis is more frequent among the late publications. The research had emphasis on the role of surface components in pathogenesis and in the immunological response of the host. For instance, immunomodulating components were described. Moreover, bacterial surface components which enhanced the viability of various bacteria by forming a protective layer were discovered.

The API is characterised by a remarkable focus on the Burkholderia species causing glanders and melioidosis. From 1990 to 2004 the publications on Burkholderia dominate and comprise about 54 % (1990-1994), 80 % (1995-99), and 76 % (2000-04), respectively. These pathogens are ranked in lower half of the group I of possible bioterrorist use by the Russians, but Western analyses do not rate these as highly likely to be used by bioterrorists. The US includes glanders in Category B in this respect, but the disease is non-notifiable and therefore not reported by the US to e.g. the World Organisation for Animal Health. According to the reviewed publications only a few additional organisms are studied at the Volgograd API, with a focus on fungal pathogens. The research on fungi is performed within the Federal Centre for Indication and Laboratory Diagnostics of Deep Mycoses and thus separated from the FIAC, at least formally. The Volgograd API has a substantial strain collection, mainly of Burkholderia. Work on Bacillus and Yersinia species at the institute indicate these are likely to be held in the collection as well.

The two institutes have routinely used animals exposed to infection by aerosol. This requires special equipment and considerable more infectious particles than other routes for infection. The frequent use of aerosol infection is also reflected by the interest in aerosol techniques and stability of aerosol particles. For instance, liposomes have been used as carriers for bacterial surface antigens, antibiotics and antiviral substances in experimental infections. The frequent use of liposomes reflects an impressive know-how in the technique. The facilities for animal experiments seem to be of a large dimension and suited for various animal species, at the Virology Centre including also primates.

The review of areas of competences reflects that the Virology Centre has a high technical competence, modern equipment is available and techniques in molecular biology have been addressed. For instance the centre has equipment for solid phase synthesis of nucleic acids which has been used for production of primers for PCR identification of Marburg and Ebola viruses. In view of that this is an institute subordinate to the Ministry of Defence and, thus, part of its production is restricted, there are achievements and competences we are unable to review here. Taken together it seems that the institute harbours a number of skilled scientists which are well suited also for the tasks of the CSDT.

According to the reviewed papers, the API seems to have more traditional research techniques and equipment for studies of bacteria. There are very few reports where molecular biology is addressed. This most likely reflects that API has a staff of skilled classical educated microbiologists, albeit with knowledge of a limited set of bacteria. The scientists of this institute have an adequate experience in areas that are relevant for the FIAC.

An important question five years after the establishment of these centres is how they fulfil the original intentions, i.e. as outlined in the decrees. In line with its founding decree, it is obvious that the CSDT performs laboratory diagnostics, isolates, characterises and stores pathogens, and there are several examples of laboratory and research work. The Centre also has the capacity to provide hospital care for patients having or suspected of having dangerous diseases at its sick bay originally built for the staff. In contrast, there is little known on the other two major responsibilities of the CSDT: The evaluation of efficiency of Russian epidemiological measures by developing mock samples and proposing improvements in diagnostics, prevention and liquidation of especially dangerous and exotic diseases. It is evident from media reports that the Centre has processed many pathogen samples, and that it has the opportunity to create an impressive strain collection of new and re-emerging pathogens. In 2004, the Centre/Virology Centre had developed about 50 “protective preparations” in the last years according to Filippov, head of the RCB Defence Force.[354]

A corresponding assessment of the FIAC can not be done according to the lack of information on its activities. This could be due to several causes. The FIAC has a strong focus on educational activities that would not be widely reported in media, or only attract attention in local media. In similar, training courses, development of normative documents and monitoring of international developments would only lead to a low number of scientific publications by the FIAC scientists. Underfunding could also contribute. Bioterrorism counter-measures have previously been known to receive low or none of the budgeted funding.

In conclusion, the Russian rhetoric on bioterrorism and the need of counter-measures are similar to the public speaking in the US. In Russia about a dozen ministries and agencies are concerned in the bioterrorism counter-measures. Different types of measures have been taken in various sectors of society and they are integrated in the existing systems for epidemiological protection and biosecurity. It was a logic measure to incorporate the new centres in well-established institutes which have been working for decades with the development of measures to prevent diseases caused by natural and deliberate spread of bacteria and viruses. Resources in terms of qualified staff, equipment and strain collections were in place. The know-how of these institutes is unique and thus a splendid source for the development of counter measures to bioterrorism.

By selecting two institutes aimed at pathogenic viruses and rickettsia (the Virology Centre) and at bacteria and fungi (the Volgograd API), respectively, the entire scale of pathogens should be covered. This is certainly true for the Virology Centre/CSDT, but can be questioned for the Volgograd API/FIAC. API has been working with a very limited set of bacteria according to its publications.

The research directions for the two centres and their mother institutes have not changed significantly over time, although bioterrorism is now a high priority in Russia. There is not a particular emphasis on Russian Group I organisms, but more of a continuous interest in viruses and bacteria which have been in focus for decades. There is only two viruses and one bacterium from the priority lists among the most frequent organisms in the publications from the two institutes; Variola and Marburg virus and Burkholderia mallei. According to the publications, a priority list deduced from the research focus of the two centres and their mother-institutes would comprise the Ebola, Variola and Marburg viruses as well as the two

[354] Russian General Describes Plan for Military, Civilian Bioterrorism Countermeasures. NTI, 18 November 2004, URL <http://nti.org/d_newswire/issues/2004_11_18.html#41726158>, accessed 22 November 2004

Burkholderia species causing glanders and melioidosis. Neither of these pathogens – with the possible exception of Burkholderias - is a real domestic problem in Russia. The conclusion is thus that according to the Russian opinion these are the top-five organisms to be used as biological warfare agents by non-state or state actors.

The two new centres are civilian as well as their aims and activities, although the CSDT is jointly subordinated to the MoD and the MoH. However, it cannot be completely ignored that their respective mother institutes were involved in both defensive and offensive biological weapons programmes in Soviet times. Russia is a states party to the Biological and Toxin Weapons Convention and has denied the existence of any offensive programme and biological weapons.[355] In this context, the unchanged focus regarding pathogens studied expertise in aerosol and research that can contribute to both defensive and offensive aims at the two new centres and their mother institutes are notable.

Contrary to the picture in the West, the scientific production from the Russian lead centres/institutes in the fight against bioterrorism is substantial reduced, at least regarding openly published papers. It is possible that some of the scientific production is classified according to the deduced potential threat from bioterrorism.

It is not possible to make a comprehensive evaluation of the outcome of the centres´ activities because there is not enough information on hand. The available pieces of information reflect that the two centres take active part in domestic outbreaks, in agreement with their decreed tasks. According to various articles in media CSDT is perfectly engaged in line with its founding decree. This gives valuable experience for handling potential future outbreaks, both natural and after the deliberate spread of infectious agents. It is more doubtful whether FIAC fulfils its role. It would be interesting in future studies of these centres to focus on their research priorities and whether any changes take place. In addition, more information is needed on the achievements and funding of the FIAC to elucidate its role and level of activities in the Russian system to combat bioterrorism.

[355] Knoph, J.T. and Westerdahl, K.S. Re-evaluating Russia's biological weapons policy, as reflected in the criminal code and official admissions. Critical Reviews in Microbiology, 32:1-13, 2006.

Agent priority list

Table 1. Russian ranking of potential bioterrorism agents

The below is a rating system of distribution of bioagents by the probability of their use as biological weapons, in accordance with the criteria listed[a] according to a system developed by domestic scientists.

Group 1 (high probability of use rating ≥ 15)		Group 2 (possible use, rating 10-14)		Group 3 (low probability of use, rating <10)	
Pathogen/Disease	Rating	Pathogen/Disease	Rating	Pathogen/Disease	Rating
Smallpox	26	Brucellosis	13	Rabies	8
Plague	23	Japanese encephalitis	13	Typhoid	7
Anthrax	21	Yellow fever	13	Dysentery	6
Botulism	21	Cholera	13	Staphylococcus	5
Viral lympocytic encephalitis		Diphtheria	12	HIV	5
Tularemia	20				
Q-fever	20				
Marburg	18				
Influenza	17				
Glanders	17				
Typhus	15				

[a]Criteria (markers):

1. human sensibility to the microbe
2. infectious dose for infection via aerosol
3. contagiousness
4. possible routes of infectiousness
5. survial in aerosol and in the environment
6. characteristics of the disease (severity, lethality, disease period, etc.)
7. possibility of mass production of the bioagent
8. possibility of rapid diagnostics
9. various means of prophylaxis
10. various means of treatment

This table is published in Kondrik EK, Volkov VYa, Kavyzina LI, Staritsyn NA, Urakov NN. Analytical Basis of the Concept of Biological Security. Obolensk, 2003, p.37, Ref 131: Vorobev, AA: Evaluation of probability of use of bioagents as biological weapons. Epidemiol. i infektsion. bolezni (Epidemiology and Infectious Diseases) No. 6, pp.54-56, 2001.

Appendix A
FOI-R--1971--SE

Publications of the Virology Center 1985-2004

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Borisevich, I.V., V.V. Mikhailov, V.P. Krasianskii, V.N. Gradoboev, E.V. Lebedinskaia, N.V. Potryvaeva, and G.D. Timan'kova. 1995. Development and study of the properties of immunoglobulin against Ebola fever. Vopr. Virusol. 40, 270-273.

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Order establishing the CSDT

Order No. 558 of the Ministry of Defence and No. 416 of the Ministry of Health about a Centre of Special Laboratory Diagnostics and Treatment of Especially Dangerous and Exotic Infectious Diseases, 20 November 1999

With the aim to improve diagnostics and treatment of especially dangerous and exotic infectious diseases, and also to co-ordinate the activity for counteracting the possibility of criminal use by terrorists, terrorist groups or terrorist organisations of pathogens of viral, rickettsial and bacterial origin, we order:

1. To create a extra-regular[1] Centre of Special Laboratory Diagnostics and Treatment of Especially Dangerous and Exotic Infectious Diseases at the Virological Centre of the Scientific-Research Institute of Microbiology of the MoD[2] of the RF[3] (in the following, the Centre of Special Diagnostics and Treatment).

2. To confirm the attached Provision about the Centre of Special Laboratory Diagnostics and Treatment of Especially Dangerous and Exotic Infectious Diseases.

3. The MoD of the RF (the Virological Centre of the Scientific-Research Institute of Microbiology of the MoD of the RF) is charged with:

    - Maintaining a laboratory base, staff and services assuring permanent preparedness to carry out laboratory diagnostics, and also for receiving persons, under surveillance for infectious pathogens of especially dangerous and exotic infectious diseases, for hospitalisation and treatment;

    - operative and qualitative fulfillment of the entrusted tasks;

    - assuring maintenance of a stockpile of diagnostics, immunobiological and medical materials.

4. The MoH[4] of the RF is charged with:

    - Placing at the disposal of the Centre of Special Diagnostics and Treatment, data on the incidence at natural foci of epidemic outbreaks caused by especially dangerous and exotic pathogens, and sufficient clinical-epidemiological information for directing probes for analysis or persons for temporary hospitalisation;

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1 The Russian termed used is ”внештатный”, meaning a subject/person outside of regular rank or staff, a free-lance subject/person and/or supernumerary. The exact meaning of this term in the context here is not entirely clear.

2 The MoD, the Ministry of Defence; this abbreviation is used in the translation to enhance readibility.

3 The RF, the Russian Federation; this abbreviation is used in the translation to enhance readibility.

4 The MoH, the Ministry of Health; this abbreviation is used in the translation to enhance readibility.

- the activity for assuring the Centre of Special Diagnostics and Treatment the required equipment, reagents, immunobiological preparations and medical materials, for the fulfillment of its tasks.

5. Control over the fulfillment of this order is entrusted to the head of the General Staff of the Armed Forces of the RF – the First Deputy Minister of Defence of the RF, and the First Deputy Minister of Health of the RF – the Sanitary Surgeon General of the RF.

Minister of Defence of the Russian Federation – Marshal of the Russian Federation
I. Sergeev
20 November 1999
No. 558

Minister of Health of the Russian Federation
Yu. Shevchenko
20 November 1999
No. 416

Provision

about the Centre of Special Laboratory Diagnostics and Treatment of Especially Dangerous and Exotic Infectious Diseases

I. General Provisions

1. This Provision defines the basic tasks and organization of activity of the Centre of Special Diagnostics and Treatment, in function at the Virological Center of the Scientific-Research Institute of Microbiology of the MoD of the RF (in the following, the Virological Center SRI Microbiology).

2. The Centre of Special Diagnostics and Treatment is a extra-regular[5] subunit of the Virological Centre SRI Microbiology intended for performing laboratory diagnostics of especially dangerous and exotic infectious human diseases of viral, rickettsial and bacteriological origin, as well as hospitalisation and treatment of persons infected (or under observation for infection) by pathogens of especially dangerous and exotic infections, and are implemented in accordance with the legislation of the RF, normative legal acts of the MoD of the RF, and this Provision.

3. Management of the activities the Centre of Special Dignostics and Treatment are implemented by the head the Virological Centre of the Scientific-Research Institute of Microbiology of the MoD of the RF.

4. The Centre of Special Diagnostics and Treatment is charged with:

   - Performing laboratory diagnostics on various pathogens of especially dangerous and exotic infections, or antibodies against these;

[5] The Russian termed used is ”внештатный”, meaning a subject/person outside of regular rank or staff, a free-lance subject/person and/or supernumerary. The exact meaning of this term in the context here is not entirely clear.

- isolation of pathogens from samples, their subsequent identification, preservation and deposition;
- hospitalisation and treatment of patients with (or persons under observation for) especially dangerous and exotic infections until diagnostically disease-free.
- development and creation of mock samples, containing pathogens of especially dangerous and exotic infections, for the evaluation of the efficiency of measures to assure the sanitary-epidemiological status of the territory of the RF;
- development of proposals for performing special laboratory diagnostics, introducing new materials and methods and their utilisation, and improving the systems of prevention and liquidation of the consequences of entry and spread of especially dangerous and exotic infectious diseases on the territory of the RF.

5. Diagnostic studies of samples from persons infected (or under observation for infection) by pathogens of especially dangerous and exotic infections, are performed in accordance with the normative acts of the MoD of the RF and the MoH of the RF for work in laboratories with a biosafety level applicable to work with microorganisms of pathogenicity groups 1 and 2.

   The basis for diagnostic studies of samples from persons infected (or under observation for infection) by pathogens of especially dangerous and exotic infections, is the permission signed by the First Deputy Minister of Health of the RF – the Sanitary Surgeon General of the RF, in agreement with the Head of the Radiological, Chemical and Biological Defence Force of the MoD of RF.

6. Hospitalisation of persons infected or under observation for infection by pathogens of especially dangerous and exotic infections, is performed at the infection section of the Virological Center SRI Microbiology in the isolation rooms [ward] with a biosafety level applicable to treating patients with infectious diseases caused by microorganisms of pathogenicity groups 1 and 2.

7. The basis for hospitalisation is the authorization by the Head of the Radiological, Chemical and Biological Defence Force of the MoD of the RF, and, in the necessity of urgent hospitalisation, a permission signed by the First Deputy Minister of Health of the RF – the Sanitary Surgeon General of the RF, in agreement with the Head of the Radiological, Chemical and Biological Defence Force of the MoD of the RF.

   The Head of the Radiological, Chemical and Biological Defence Force of the MoD of the RF reports on the status of hospitalisation to the Head of the General Staff of the Armed Forces of the RF – the First Deputy Minister of Defence of the RF.

8. In all cases when pathogens of especially dangerous and exotic infections are isolated from samples from persons delivered or selected for hospitalisation, the Head of the Centre for Special Laboratory Diagnostics and Treatment of Especially Dangerous and Exotic Infectious Diseases, immediately reports to the Head of the Radiological, Chemical and Biological Defence Force of the MoD of the RF, and notifies the First Deputy Minister of Health of the RF – the Sanitary Surgeon General of the RF; the Head of the Radiological, Chemical and Biological Defence Force of the MoD of the

RF reports to the to the Head of the General Staff of the Armed Forces of the RF – the First Deputy Minister of Defence of the RF.

In the case of isolation of pathogens of especially dangerous and exotic infections from delivered samples, the head of the Centre for Special Laboratory Diagnostics and Treatment of Especially Dangerous and Exotic Infectious Diseases presents to the Head of the Radiological, Chemical and Biological Defence Force of the MoD of the RF, and the First Deputy Minister of Health of the RF – the Sanitary Surgeon General of the RF, a written account of the performed laboratory studies and treatment of infected persons.

II. Special Laboratory Diagnostics

9. Special laboratory diagnostics of diseases of especially dangerous and exotic infections are carried out in two stages depending on the aim and type of sample delivered for analysis:

   First stage – by application of rapid immunochemical and/or molecular biological methods,

   Second stage – by isolation and typing of pathogen cultures by virological or bacteriological methods.

   The choice of methods for performing laboratory studies of delivered samples, is the responsibility of the specialists of the Centre for Special Diagnostics and Treatment.

III. Hospitalisation and Treatment

10. Persons under observation for infection with pathogens of especially dangerous and exotic diseases are subject to hospitalisation at the Centre for Special Diagnostics and Treatment. Samples are taken from all persons received, for laboratory analysis (unless they have been taken at a previous stage of evacuation and not subjected to analysis at the Centre for Special Diagnostics and Treatment).

11. Therapy begins after receiving the persons at the infection section of the Centre for Special Diagnostics and Treatment. The strategy of treatment is selected from the normative documents of the MoH of the RF and the MoD of the RF, as well as data in the special scientific literature.

12. The treatment is performed by physicians-specialists of the infection section of the Centre for Special Diagnostics and Treatment, with the consultative support from, when necessary, the leading specialists of the MoH of the RF.

13. Hospitalisation and treatment at the Centre for Special Diagnostics and Treatment is performed until establishment of a final diagnosis. In correspondance with the results of laboratory diagnostics of the etiological agent of especially dangerous and exotic diseases, the hospitalised persons are directed to further treatment and rehabilitation at the medical establishment of the MoH of the RF or other federal executive organs.

IV. Organisation and Guranteeing the Activities at the Centre for Special Diagnostics and Treatment

14. The functioning of the Centre for Special Diagnostics and Treatment is guaranteed by the co-workers of the Virological Centre SRI Microbiology, who are directed [appointed] by order of the Head of the Virological Center of the Scientific-Research Institute of Microbiology of the MoD of the RF, corresponding to the amount of work.

15. The results of the performed studies are communicated to other organisations only after a decree by the Head of the General Staff of the Armed Forces of the RF – the First Deputy Minister of Defence of the RF, and the First Deputy Minister of Health of the RF – the Sanitary Surgeon General of the RF.

16. At the Centre for Special Diagnostics and Treatment a never-decreasing stock-pile of immunobiolgical and medical materials, necessary for the maintainnance of a constant preparedness to fulfill the entrusted tasks. The brands and volumes of stored materials, as well as the instruction for their use, and the replacement is determined by the Head of the Virological Center SRI Microbiology, in agreement with the First Deputy Minister of Health of the RF – the Sanitary Surgeon General of the RF.

17. Payment of the expenses for diagnostics and medicines is charged to the account of the Centre for Special Diagnostics and Treatment, by the establishments of the MoH of the RF, which have directed persons infected (or under observation for infection) by pathogens of especially dangerous and exotic infections for analysis of samples, as well as for hospitalisation and treatment.

Head of the general Staff of the Armed Forces of the Russian Federation – First Deputy Minister of Defence of the Russian Federation – General of the Army

A Kvashnin

First Deputy Minster of Health of the Russian Federation – Sanitary Surgeon General of the Russian Federation

G. Onishchenko

Appendix C
FOI-R--1971--SE

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Order establishing the FIAC

Ministry of Health of the Russian Federation, Order No. 300 "On Establishing a Federal Interagency Center", dated July 30, 1999

For the purpose of establishing a uniform basis for the Interagency Committee on evaluation and testing of new means and methods of indication of pathogens of especially dangerous infections, hereby I order:

1. To organize a Federal Interagency Center for training specialists, testing means and methods of indication of pathogens, causing extremely dangerous infections, to be located in the facility of the Volgograd Scientific Reserach Anti-Plague Institute, on a functional basis (Appendix).

2. To appoint N.G. Tikhonov, the Director of the Volgograd Scientific Research Institute, as a Chief Manager of the Federal Center.

3. G.G. Onishchenko, the First Deputy Minister, shall bear responsibility for the control over the execution of the order.

Minister of Health
Yu. L. Shevchenko

Appendix:

Statutes of the Federal Interagency Centre for Preparation of Experts, Tests of Means and Methods for Indication of Pathogens of Especially Dangerous Infections

I. General provisions.

1.1. The Federal Interagency Centre of preparation of experts, tests of means and methods of indication of pathogens of especially dangerous infections (in the following, the Federal Centre) is the interdepartmental coordinating, advisory-methodical, educational, diagnostic and expert body which also carries out functions of lead establishment on issues of indication and express-diagnostics of potential agents of bioterrorism.

1.2. The Federal Centre of the Ministry of Health of Russia is created and functions on the basis of the structural divisions and laboratories of the Volgograd Research Anti-Plague Institute according to the present order in accordance with the decision of the Federal Anti-terrorist Commission (FAK) of 16.02.99.

1.3. The activity of the Federal Centre is carried out according to federal laws, decrees and orders of the President of the Russian Federation, Decisions of the Government of the Russian Federation, the Concept of activity of the federal enforcement authorities which are included in system specially of authorized bodies of the Russian Federation, in the field of preservation of the environment and health of the population, and also other interested ministries and departments in extreme situations caused by acts of terrorism; also, it is regulated by sanitary legislation in force, orders and decisions of the Ministry of Health of Russia, the Charter of the Volgograd Research Anti-Plague Institute and the present Regulations about the Federal Centre.

1.4. The Federal Centre carries out the activity in interaction with the Federal Sanitary-Epidemiological Monitoring Service centres and the Anti-Plague establishments of the Ministry of Health of Russia, and also the interested establishments of other ministries and departments.

1.5. The head of the Federal Centre is appointed and released by order of the Ministry of Health of Russia.

1.6. Aiming at joint decisions on questions of the Federal Centre's activities, a scientific and technical council for the head of the Centre is created, into which representatives of the interested ministries and departments are included along with employees of the Centre.

1.7. The Federal Centre is financed by Ministry of Health of Russia from the federal budget. A source of financing of activity of the Federal Centre are also unappropriated means.

1.8. The Federal Centre has special forms in which are specified its name, post and cable addresses, phone numbers, a fax and e-mail.

II. Tasks and functions of the Federal Centre.

2.1. Primary goal: Counteracting biological terrorism and protection of the population against possible use by terrorists, terrorist groups or terrorist organizations of biological means of mass destruction. The tasks, connected to organization the interaction of establishments of the ministries and departments, are part of the development of antiterrorist actions. The functions of the Federal centre are:

2.2. Training of experts in indication and express-diagnostics of pathogens of especially dangerous infections (EDI) for the purposes of counteraction to bioterrorism in courses for specialization and improvement of professional skill of doctors and laboratory technicians, issuing certificates of the established form. Development and improvement of course curricula.

2.3. Creation of a uniform base for the Interagency Committee on evaluation and tests of new means and methods of indication and express-diagnostics of various pathogens. Development and improvement of instructive-methodological documents for the realization of the Interagency Committee on testing. The introduction of necessary changes into the indication scheme for pathogens of EDI in view of the latest data, including by genetic and biosensor diagnostics.

2.4. Performance and coordination NIR [possible expansion: scientific-research work] on development and inclusion in the indication scheme for pathogens of EDI, of modern methods, including molecular genetic, and also NIR [possible expansion: scientific-research work] on designing and introduction in practice of the automated systems based on bioimmunosensors, magnetoimmunosorbents, chemiluminiscence analysis, etc. The analysis of modern achievements of domestic and foreign science and the choice of future directions of scientific development in the field of indication and express-diagnostics of pathogens of EDI.

2.5. Creation of a database and to supply information on the activity of the Federal Centre and the interested establishments on questions of bioterrorism. Annual reporting [registration] of the appropriate analytical information to Working Group No. 3 of FAK.

2.6. Rendering the organizational and methodological help to establishments of practical public health services and Federal Sanitary-Epidemiological Services, on the questions where the Federal Centre is competent.

2.7. Realization, as agreed with Ministry of Health of Russia, of seminars, meetings, and scientific-practical conferences on questions of bioterrorism counteraction with the publication of materials when due hereunder.

2.8. Development of organizational bases of interaction with the establishments of the Ministry of Health of Russia, the Ministry of Internal Affairs of Russia, the FSB of Russia, the Ministry of Defence of Russia, the Ministry of Agriculture and Food Production of Russia and other interested ministries and departments in assuring security measures at facilities that are carrying out work with potentially dangerous bioagents.

The Head of Department
of Goskomsanepidnadzor

A.A. Monisov

Appendix E
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List of abbreviations

API	Anti-Plague Institute
BCW	Biological and chemical weapons
BL-3	Biosafety level 3 (i.e. the next to the highest safety level in the West)
BL-4	Biosafety level 4 (i.e. the highest safety level in the West)
BTWC	Biological and Toxin Weapons Convention
BW	Biological weapons
CBMs	Confidence-Building Measures
CCHF	Congo-Crimean hemorrhagic fever
CSDT	Centre of Special Laboratory Diagnostics and Treatment of Especially Dangerous and Exotic Infectious Diseases
EDI	Especially dangerous infections
EEE	Eastern equine encephalitis
FAB	Fragments of immunoglobulins
FAK	Federal Antiterrorist Committee
FIAC	Federal Inter-Agency Centre for training specialists, and testing means and methods of indication of pathogens causing extremely dangerous infections
FSB	Federal Security Service
Mab	Monoclonal antibodies
MoD	Ministry of Defence
MoH	Ministry of Health
OHF	Omsk hemorrhagic fever
PCR	Polymerase chain reaction (a method to synthesise short fragments of DNA)
PSI	Proliferation Security Initiative
RCB	Radiological, Chemical and Biological
Rospotrebnadzor	Federal Service for Consumer Rights and Human Wellbeing
SARS	Severe acute respiratory syndrome
SRI	Scientific Research Institute
TBE	Tick-borne encephalitis
VEE	Venezuelan equine encephalitis
WHO	World Health Organisation
WMD	Weapons of mass destruction